

Exhibits 1, 2, 5, 8, 10, 13, 15- 22, 26, 29, & 31

ZHP has designated the above exhibits as confidential. Plaintiffs are in the process of meeting and conferring with ZHP on the propriety of these designations. In accordance with the Court's Confidentiality and Protective order, Plaintiffs will forward the Exhibits to the Court directly via email for its in camera review.

Exhibit 3

Establishment Inspection Report
Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

TABLE OF CONTENTS

Summary.....	2
Administrative Data.....	3
History.....	4
Interstate Commerce.....	5
Jurisdiction.....	5
Individual Responsibility and Persons Interviewed.....	5
Firm's Training Program.....	6
Manufacturing Operations.....	6
Quality.....	6
PRE-APPROVAL [REDACTED].....	10
Objective 1: Readiness for Commercial Manufacturing.....	10
Objective 2: Conformance to [REDACTED].....	11
Objective 3: Data Integrity Audit.....	11
Facilities and Equipment.....	11
Materials Management.....	12
Production.....	13
Laboratory/Design Operations.....	16
Manufacturing Codes.....	18
COMPLAINTS.....	19
RECALL PROCEDURES.....	19
Objectionable Conditions and Management's Response.....	21
Refusals.....	51
General Discussion with Management.....	51
Additional Information.....	51
logistics.....	51
Samples Collected.....	52
Voluntary Corrections.....	54
Exhibits Collected.....	54
Attachments.....	57

David Chesney

16

3/21/2022 - MOP

1 of 58

Min Li

ZHP-312

4/21/2021

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

SUMMARY

This foreign comprehensive For Cause inspection of an API (Active Pharmaceutical Ingredient) manufacturer was conducted in accordance of CPGM 7352.832 [REDACTED] Pre-Approval Inspections/Methods Validation, Drug Manufacturing Inspections, CPGM 7356.002F Active Pharmaceutical Ingredient Process Inspections, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients ICH (International Conference on Harmonization Regulations) Q7, FY18 (Fiscal Year 2018) Foreign Drug Inspection assignment MARCS ID # 98345, and FACTS ID# 9501248 issued by IOG (Trip # 2018-318D) to determine compliance status. The inspection is reported under PAC (Program/Assignment Code) 52832. The inspection included coverage of profile class CSN (Non-sterile Active Pharmaceutical Ingredient by Chemical Synthesis).

The previous inspection dated May 2017 concluded with the issuance of a three item Form FDA 483, Inspectional Observations for: 1) failure to investigate OOS/OOT, 2) failure to appropriately maintain equipment, and 3) OOS results invalidated without scientific justification. The previous inspection was initially classified OAI (Official Action Indicated) and reclassified VAI (Voluntary Action Indicated). Corrective actions were not adequate.

APIs covered include: Valsartan, Levetiracetam, and Tadalafil. The following systems were covered: Quality, Facilities and Equipment, Production, and Laboratory Control. Partial coverage was given to the Material System. The Packaging and Labeling System was not covered. Inspectional coverage for Tadalafil included verification of readiness for commercial manufacturing, conformance to [REDACTED], and data integrity audit. Batch production records, laboratory records, training records, logbooks, protocols, procedures, deviation investigations, change control, and stability study data were reviewed.

A Form FDA 483, Inspectional Observations, was issued at the close of the inspection for: 1) inadequate change control system; 2) inadequate validation program; 3) insufficient investigation of critical deviations; 4) the quality unit does not always fulfill the responsibilities of the quality unit; 5) cleaning procedures do not have sufficient detail; 6) equipment is not always of appropriate design; 7) preventive maintenance procedures are not always adequate; 8) lubricants, heating fluids and coolants are not always food grade lubricants and oils; 9) sampling plans are not always scientifically sound; 10) stability studies are not always adequate; and 11) production deviations are not always thoroughly investigated. There were no refusals. Samples were collected during this inspection, see the sample collection section of this report for details.

Management was warned failure to make corrections could result in regulatory action without further notification including but not limited to a warning letter or import detention. Management

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

did not agree with the observations. Management did not commit to making corrections. Mr. Jun Du, Executive Vice President, committed to submitting a written response to the U.S. Food and Drug Administration (FDA) within 15 business days.

ADMINISTRATIVE DATA

Inspected firm: Zhejiang Huahai Pharmaceutical Co., Ltd.

Location: Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai 5th Avenue
Linhai, Taizhou Zhejiang, 317016 China

Phone: +86 576 85016003

Mailing address: Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai 5th Avenue
Linhai, Taizhou Zhejiang, 317016 China

Dates of inspection: 07/23/2018-07/28/2018, 07/30/2018-08/03/2018

Days in the facility: 11

Participants: Cheryl Clausen, Investigator and Joel Hustedt, Investigator

This inspection was supported by Lili Sang (during the period of 07/23/2018 – 07/28/2018), who is a Locally Engaged Staff (LES) hired by the United States Embassy in Beijing and assigned to FDA to work in support of FDA activities. All information, including documents collected during this inspection and any translation from local language to English by Lili Sang (LES) that supports the Form FDA 483, Inspectional Observations (if Form FDA 483 was issued) and the Establishment Inspection Report (EIR) was collected in collaboration with the FDA investigator(s).

On July 23, 2018 at Zhejiang Huahai Pharmaceutical Co., Ltd., Mr. Hustedt and I showed our credentials to Mr. Jun Du, Executive Vice President. Mr. Du stated he is the most responsible person at the facility. Mr. Jie Wang, Vice President Business Development Headquarters, provided an informational presentation. **Exhibit 132** is a list of those present for the opening meeting. On August 3, 2018, a Form FDA 484, Receipt for Samples, was issued to and signed by Mr. Du; and a Form FDA 483, Inspectional Observations, was issued to Mr. Du.

Post inspection correspondence should be addressed to: Mr. Jun Du, Executive Vice President, Zhejiang Huahai Pharmaceutical Co., Ltd., Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai 5th Avenue, Linhai, Taizhou Zhejiang 317016 China.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

This was a team inspection consisting of Cheryl A. Clausen, Lead Investigator and Mr. Joel Hustedt, Investigator. Mr. Hustedt was present 07/23/2018-07/28/2018. This report was written by Investigator Clausen (CAC) with sections written by Mr. Hustedt (JDH).

Translation was provided by: Mr. Zi-Qiang Gu, Ph.D., Pharmaceutical Consultant (07/23/2018 – 07/26/2018); and Mr. Wayne Cheng, Deputy QA Manager (07/26/2018, 07/30/2018 – 08/03/2018).

Representatives from the local government present during this inspection and dates present include: Mr. Xu Dan, Division of Drug and Cosmetic Inspection, Inspector (07/23/2018-07/27/2018); Ms. Chen Liu, Zhejiang Center for Drug Certification & Inspection, Technical Officer (07/23/2018-07/27/2018); Mr. Peng Wang, Safety Supervisor Department of Taizhou Market Supervision Administration, Deputy Director (07/23/2018-07/28/2018, 07/30/2018-08/03/2018); Ms. Bo JU, Zhejiang FDA, Commissioner (07/28/2018, 07/30/2018-08/03/2018); Mr. Weidong Wang, Zhejiang Center for Drug Inspection, Supervisor (08/03/2018); Mr. Xingfu YE, Taizhou Market Supervision Administration, Deputy Director General (08/03/2018); and Mr. Hailen Chen, Safety Supervision Department of Taizhou Market Supervision Administration, Director (08/03/2018).

HISTORY

Zhejiang Huahai Pharmaceutical Co., Ltd. is a limited liability company established in 1989. Corporate headquarters are located at: Zhejiang Pharmaceutical Co., Ltd. Xunqiao, Linhai, Zhejiang 317024 China (FEI: 3003999190). Manufacturing operations occur at headquarters and this site. Subsidiary Zhejiang Pharmaceutical Co., Ltd. Duchuan Road, Duqiao, Linhai, Zhejiang 317016 China manufacture intermediates only. Zhejiang Huahai Pharmaceutical Co., Ltd. does not have a history of regulatory action. The firm is currently the subject of a recall for Valsartan initiated shortly before the start of this inspection. Please refer to the Recall section of this report for further information.

The firm operates 7 days a week 24 hours a day. Business offices are open 8:00 AM – 5:30 PM. Plant shifts are 7:30 AM – 3:30 PM, 3:30 PM – 11:30 PM, and 11:30 PM – 7:30 AM. The firm does not have planned periods for extended shutdown. The firm has 2,042 full time employees including 1,338 involved in manufacturing operations, 185 involved in quality operations, and 519 involved in other activities.

The firm's drug registration is current for 2018. **Exhibit 136** includes an aerial view of the site layout.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

INTERSTATE COMMERCE

Zhejiang Huahai Pharmaceutical Co., Ltd. commercially manufactures APIs intended for use in the manufacture of finished dosage drug products shipped to the U.S. The firm transports finished APIs by truck and then air to foreign finished dosage drug manufacturers who then ship finished dosage drug products to the U.S. **Exhibit 137** is a list of consignees manufacturing finished dosage drug products for shipment to the U.S.

Valsartan batches C5355-18-009M, C5355-18-010M, C5355-18-011M, and C5355-18-012M were shipped to fulfill Purchase Order (PO) 4500653172 placed February 1, 2018 [**Exhibit 140 page 1**]. Packing List for Invoice No. HH2018329 includes Valsartan batches C5355-18-009M, C5355-18-010M, C5355-18-011M, and C5355-18-012M date February 5, 2018 [**Exhibit 141 page 6**]. Airwaybill FGSAE18020011 for PO number 4500653172 placed February 1, 2018 shows the shipment was received February 7, 2018 at Sunoble International Cargo Services Inc. in Shanghai, China for shipment to Novartis Pharma Stein AG located at Schaffhauserstrasse 101, Werk Stein Bau 190 4332 Stein, Switzerland [**Exhibit 140 page 7**]. Zhejiang Huahai Pharmaceutical Co., Ltd. Commercial Invoice No. HH2018329 was issued February 5, 2018, for PO number 4500653172 [**Exhibit 140 page 8**].

Exhibit 187 lists the batch numbers for Valsartan batches shipped to consignee Torrent Pharmaceuticals Ltd. located in Ahmedabad, India.

JURISDICTION

Zhejiang Huahai Pharmaceutical Co., Ltd. manufactures APIs subject to portions of the Food, Drug, and Cosmetic Act. **Exhibit 138** is a list of products manufactured at this site. **Exhibit 139** lists Valsartan shipments 2016-2018 shipped to finished dosage manufacturers intended for further manufacture and shipment to the U.S. **Exhibit 141** includes labels and labeling for Valsartan batch C5355-18-009M.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Mr. Jun Du, Executive Vice President - Mr. Du is overall responsible for site operations including correcting cGMP deficiencies. **Exhibit 133** is a job description for Mr. Du. Mr. Du reports to Mr. Bauhua Chen, President, located at Zhejiang Huahai Pharmaceutical Co., Ltd. headquarters in Xunqiao. Mr. Du was present for the opening meeting, daily wrap-up discussions, and the close out meeting.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

Ms. Jucai GE, QA Director - Ms. GE is responsible for all quality assurance functions including preventing GMP violations. **Exhibit 134** is a job description for Ms. GE. Ms. GE reports to Mr. Jenson YE, QA Vice President Headquarters. Ms. GE was present throughout the inspection, answered questions, provided documents, and was present for the opening meeting, daily wrap-up discussions, and the close out meeting.

Various other individuals assisted and were interviewed throughout the inspection. **Exhibit 135** is a list of Directors as of July 24, 2018. **Exhibit 136** includes an organizational chart. The firm's U.S. Agent is: Mr. Xiaodi Guo, PhD., Executive Vice President, HuaHai U.S. Inc., Cranbury, New Jersey 08512; phone 609-655-1688, email xguo@huahaipharmus.com.

FIRM'S TRAINING PROGRAM

The firm has a written training procedure requiring at least annual GMP training. Training is evaluated through written examination. Trainees are required to answer at least 75% of the questions correctly. Employees scoring below 75% are retrained. I reviewed training records for: Shelei Feng, QC Analyst; Weifeng Yang, Production Operator; and Chenglong Shan, Maintenance. Nothing remarkable was noted.

MANUFACTURING OPERATIONS

The firm does not use any new or unusual components, raw materials, or equipment. The manufacturing process for Valsartan, USP consists of dispensing, distillation, condensation, filtration, crystallization, centrifugation, drying, milling, and packaging. Manufacturing suites and equipment used in the manufacture of Valsartan, USP are dedicated. **Exhibit 143** is list of dedicated equipment used in the manufacture of Valsartan in each Workshop. Manufacturing suites and equipment used in the manufacture of Tadalafil are not dedicated. **Exhibit 142** is the equipment list for non-dedicated Workshop 5 with the APIs manufactured using each piece of equipment.

Mr. Jun Du, Executive Vice President, stated Novartis placed an order for 45 Metric tons of Valsartan early in 2018. **Exhibit 145** is the POs (Purchase Order) from Novartis for fulfillment of the order. **Exhibit 144** is the Invoices the firm issued for the POs from Novartis.

QUALITY

Zhejiang Huahai Pharmaceutical Co., Ltd. has an established Quality Unit consisting of the Quality Assurance department and the Quality Control laboratories. The firm has established written procedures for the quality unit covering supplier qualification, training, batch release, validation,

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

calibration, investigations including deviations and Out-of-Specification (OOS), product recall, stability studies and complaints. Throughout the inspection, I observed employee practices, reviewed documents, and conducted personal interviews with various staff members to assess whether the firm's quality system is designed to achieve sufficient control over the facility and commercial manufacturing operations. Through these activities, I observed the Quality Unit is involved in activities including but not limited to: review of manufacturing documents and approval of product prior to release; qualification and validation activities; deviations and investigations; and change control activities.

The firm has a written procedure for Annual Product Quality Review (APQR) Management System SMP-020.06 effective November 15, 2017 [**Exhibit 173**]. The firm's APQR procedure is silent regarding conducting year-to-year trending to identify potential shifts in the manufacturing process. I reviewed the APQR for Valsartan Workshop 2 East C5355 December 25, 2015 to December 24, 2016. The firm does not conduct year-to-year trending to identify potential shifts in the manufacturing process.

The quality unit does not always fulfill the responsibilities of the quality unit to release or reject all APIs (**FDA Observation 4**). The quality unit does not always demonstrate the firm has the written procedures necessary to conduct deviation investigations and/or the firm's quality unit has the authority and responsibility to ensure all critical deviations are thoroughly investigated (**FDA Observation 3a, 3bi, 3bii, 3biii, 3c, 3d, and 3e**). The firm does not have an adequate change control system to evaluate changes that may impact intermediates and APIs (**FDA 483 Observation 1ai, 1aii, 1bi, 1bii, 1c, and 1d**). Risk assessments are not always thorough or documented. The firm initiates commercial scale changes based on lab scale research projects.

Ongoing deviation investigation for Deviation Number DCE-18001 was initiated June 6, 2018, for a suspected genotoxic impurity in Valsartan [**Exhibit 113**]. The firm's customer (Novartis) informed the firm the customer identified a small unknown peak after the Toluene peak during residual solvent testing using a GC-FID instrument that led the customer to send samples to a third-party laboratory for identification of the unknown peak (the third-party laboratory identified the unknown peak as NDMA (N-Nitrosodimethylamine)) [**Exhibit 113 page 1 Section Description**]. The Deviation Report for Deviation Number DCE-18001 prepared July 20, 2018, states the presence of trace amounts of NDMA in the final Valsartan API requires the convergence of the following three factors: i) use of dimethylformamide in the tetrazole formation step, ii) quenching of azide using nitrous acid, and iii) quenching takes place in the presence of the product [**Exhibit 113 page 20**]. I asked Mr. Min Li, Ph.D. (Bio-organic and Analytical Chemistry), Vice President Analytical Operations Headquarters, if the firm recreated the circumstances of the firm's hypothesis and then conducted tests to verify the firm's hypothesis regarding the formation of NDMA in Valsartan API. Dr. Li stated it was not necessary to do that because based on the firm's knowledge and experience everyone retrospectively agrees this is the cause and the firm conducted a lab scale test for Valsartan

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

API produced separate from the quenching step and did not find NDMA in the Valsartan API produced from a separate quenching step. Dr. Li stated the firm would recreate the circumstances stated in the firm's hypothesis to verify the hypothesis. No information was provided before the close of this inspection regarding the outcome of the firm's test to confirm the firm's hypothesis.

I asked Dr. Li if the firm tested the firm's other sartan type finished APIs for NDMA. Dr. Li stated the firm tested other sartan type finished APIs manufactured by the firm and did not find NDMA. Dr. Li stated the firm did a reverse study where the firm separated the intermediate Valsartan crude from the quenching step on a lab scale and no NDMA formed.

I asked Dr. Li if the firm evaluated the contribution of batch size and the impact of batch size on the variation in the concentration of NDMA between the different workshops. Dr. Li stated the firm has not looked at this. Dr. Li stated the firm will look into this to evaluate the impact.

In Deviation Report for Deviation Number DCE-18001, the firm states NDMA will not be generated in Valsartan batches manufactured using Process I or Process II (Triethylamine(TEA)), since no DMF is used [**Exhibit 113 page 43**]. On August 1, 2018, I asked Mr. Du if the firm tested Valsartan API manufactured for the Chinese market using Process II (TEA) manufacturing process for NDMA and if so, the results of those tests. On August 2, 2018, Mr. Du stated the firm tested Valsartan API manufactured for the Chinese market using Process II (TEA) manufacturing process and found from 11 ppm to 107 ppm NDMA in the batches tested. I asked Mr. Du if the firm planned to re-evaluate the firm's hypothesis or if the firm planned to continue the current process validation to separate the Valsartan intermediate product from the quenching step in chemical synthesis step 4. Mr. Du stated the firm plans to continue the current process validation to separate the Valsartan intermediate product from the quenching step in chemical synthesis step 4. **Exhibit 114** shows a comparison of Valsartan Triethylamine Hydrochloride Process Parameters manufactured for the US market and the Chinese market.

Dr. Li stated it is not scientifically possible to remove NDMA by recrystallization. In Deviation Report for Deviation Number DCE-18001, the firm states all returned and quarantined Valsartan API batches will be reprocessed and tested against revised specification (< 0.3 ppm NDMA) [**Exhibit 113 page 45**]. DMF# 23491 Valsartan, USP (Process II) includes one option for reprocessing the drug substance, recrystallization [**Exhibit 115**].

From January 2016 to July 2018 the firm rejected a total of 15 batches of APIs and received a total of 7 batches of APIs manufactured for the US market [**Exhibit 186**]. I asked Ms. GE if the firm reprocessed all rejected and returned APIs. Ms. GE stated yes. I asked Ms. GE if the firm conducts additional impurity testing on rejected and returned batches. Ms. GE stated no. I asked Ms. GE if the firm evaluated the potential risk of introducing unknown impurities into the firm's

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

manufacturing Workshops from reprocessing rejected and returned batches. Ms. GE stated the finished APIs meet product release testing specifications.

The firm has a written procedure Reprocess and Rework Management Procedure SMP-025.3 effective January 30, 2018 [Exhibit 171]. Exhibit 171 page 7 section 5.5 specifies an “R” or a “W” is added to the batch number so the batch number can be traced to the original batch. However, the final API batch number after reprocessing does not indicate the batch was reprocessed. I asked Ms. Yuelin Hu, Assistant Director QA, if the final API batch number indicates whether a batch has been reprocessed. Ms. Hu stated no. Exhibit 171 page 7 section 5.7.2 specifies a risk assessment is used to determine whether the reprocessed batch is added to the firm’s stability study program. Ms. GE stated the first reprocessed batch is added to the firm’s stability study program. I asked Ms. GE if she meant only the first reprocessed batch is added to the firm’s stability study program. Ms. GE responded yes.

I reviewed the Stability Protocol for Valsartan, USP CS-12-005 implementation date January 11, 2012. All data reported was within specification. Results were similar across U.S. and non-U.S. markets.

Validation of production processes, cleaning procedures, and analytical methods is not always adequate (FDA 483 Observation 2a, 2bi, 2bii, 2bii, 2c, 2d, and 2e). Valsartan Impurities Profile Analysis Report-01 written April 10, 2012 [Exhibit 176] is an example of the firm’s process for evaluating impurities in final APIs. Due to time constraints, I did not review the impurity profile for all APIs intended for manufacture of finished dosage drug products shipped to the U.S. I asked Ms. GE if the impurity profile for Valsartan would be representative of the impurity profiles for all final APIs manufactured at the firm. Ms. GE stated yes.

I asked Mr. Peng Dong, Deputy Director East Zone, if the firm added controls to minimize NDMA in Valsartan for: raw materials, intermediates, and/or solvents; equipment operating conditions; IPC (In-process Control) testing; stability studies; hold times; or storage conditions. Mr. Dong stated no. Mr. Dong stated the firm’s optimized process will eliminate NDMA in Valsartan so there is no need for additional controls. I asked Mr. Dong if the firm has data comparing the concentration of NDMA in reprocessed Valsartan batches and Valsartan batches that have not been reprocessed. Mr. Dong stated no.

Process Validation Protocol Zinc Chloride Process of Valsartan Workshop II CNVP-11-075 includes a specification for Valsartan intermediate crude Related Substance by HPLC for impurity peak, Pentacylated Deformylation Compound at $RRT\ 1.7 \leq 1.0\%$ [Exhibit 102]. The final Valsartan API does not have a specification for Related Substance by HPLC at $RRT\ 1.7 \leq 1.0\%$. I asked Mr. Dong if the same Related Substance by HPLC test method is used to test both the intermediate crude

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

Valsartan and the final Valsartan API. Mr. Dong stated yes. I asked Mr. Dong why the final Valsartan API does not include a specification for Related Substance by HPLC at RRT $1.7 \leq 1.0\%$. Mr. Dong stated in the final Valsartan API this impurity peak is controlled in the single unspecified impurity (specification $\leq 1.0\%$). I asked Mr. Dong how long the firm has been aware of an impurity at RRT $1.7 \leq 1.0\%$. Mr. Dong stated the firm has been aware of an impurity at RRT 1.7 since the manufacturing process for Valsartan was first developed in-house in 2008. I asked Mr. Dong for the concentration range of impurity peak at RRT 1.7 in intermediate crude Valsartan for the TEA process and the DMF process. Mr. Dong stated the concentration range for this impurity peak for the TEA process is 0.2% to 0.6% and $< 0.2\%$ for the DMF process.

PRE-APPROVAL [REDACTED]

The firm's readiness for commercial manufacturing of the API in the following [REDACTED] was assessed: [REDACTED]. Zhejiang Huahai Pharmaceutical Co., Ltd. is listed in the [REDACTED] as the manufacturer of Valsartan, USP API. The three primary inspectional objectives of the preapproval inspection program were covered during this inspection.

OBJECTIVE 1: READINESS FOR COMMERCIAL MANUFACTURING

I reviewed the firm's written procedures and protocols for batch release, change control, deviations, complaints, sampling, testing, qualification, validation, and the drug development report. Tadalafil Impurity Profile Analysis Report indicates the firm will test the first three batches each year for genotoxic impurity Methyl Chloroacetate and the firm will not include testing of Methyl Chloroacetate in product release testing. I asked Mr. Dong if the final Tadalafil API release testing will include testing for genotoxic impurity Methyl Chloroacetate. Mr. Dong stated no.

The firm does not have adequate systems in place for change control, investigation of deviations, sampling or validation (**FDA 483 Observations 1, 2, 3, 9**). Cleaning procedures do not include sufficient detail to ensure equipment is cleaned in a reproducible and consistent manner (**FDA 483 Observation 5**). The firm does not take and test rinse samples from each reactor. The firm takes one rinse sample at the end of the equipment train and tests the rinse sample for TOC (Total Organic Carbon). The firm does not test rinse and/or swab samples for product residue, product degradants, solvent residue, or solvent degradants. I asked Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, if the firm tests rinse and/or swab samples for product residue, product degradants, solvent residue, or solvent degradants. Mr. Q. Li stated no the firm tests for TOC because a TOC test gives the firm information regarding the presence of any organic carbons. I asked Mr. Q. Li if the firm has data showing TOC testing can identify specific impurities and/or degradants. Mr. Q. Li stated no.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

The firm does not ensure coolants are food grade (**FDA 483 Observation 8**). Equipment is not always adequate for intended use (**FDA 483 Observation 6b and 6c**). The firm's stability study program is not adequate (**FDA 483 Observation 10**).

The firm commercially manufactures Tadalafil for non-US markets in Workshop W05. I verified proposed commercial processes and manufacturing batch records. I reviewed an executed batch record. During packaging the firm passes the final API through a ferrous metal detector. I asked Ms. GE why the firm does not use both a ferrous and non-ferrous metal detector. Ms. GE stated if a non-ferrous metal is present the firm will see the anomaly. I asked Ms. GE how the firm will detect sub-visible non-ferrous metal particles. Ms. GE understood the question, she acknowledged the question, but she did not provide a verbal response. I reviewed the firm's written procedure for vendor qualification and vendor qualification forms. I observed employee practices, reviewed documents, and conducted personal interviews with various staff members to evaluate the effectiveness of the firm's quality system and the ability of quality to control the facility and commercial operations.

OBJECTIVE 2: CONFORMANCE TO [REDACTED]

I conducted personal interviews with various staff members to assess whether the firm's proposed commercial manufacturing operations are consistent with the [REDACTED]. The proposed commercial scale is the same size as the exhibit batches submitted in the [REDACTED]. I verified the formulation is consistent with the [REDACTED]. I reviewed the product development report for Tadalafil. Nothing remarkable was noted.

OBJECTIVE 3: DATA INTEGRITY AUDIT

I observed employee practices, instrument calibration and usage logbooks, electronic records and conducted personal interviews with various staff members to verify the firm's current practices. I verified the firm has the necessary instruments to conduct required testing for the approval and release of the finished product. Laboratory instruments are qualified and calibrated. I reviewed raw data submitted as part of the firm's drug [REDACTED] for product release testing and stability study testing. Nothing remarkable was noted.

FACILITIES AND EQUIPMENT

The manufacturing facility is a non-dedicated manufacturing facility. No highly sensitizing, cephalosporins, teratogens, cytotoxic materials, beta-lactams, non-penicillin beta-lactams, steroids, hormones, pesticides, or other non-pharmaceutical chemicals are manufactured at this facility. The

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

firm has specifically designed areas for manufacturing operations. No deficiencies were noted regarding lighting, potable water, toilet facilities, sewage and refuse disposal; or the use of other rodenticides, fungicides, insecticides, cleaning and sanitizing agents.

The firm has written facility cleaning and maintenance procedures. The firm has an on-going preventive maintenance program. The firm regularly cleans the facility.

The facility layout is designed to control the flow of people and materials through the manufacturing area. General air handling systems are in place. Pressure differentials between the corridor and manufacturing suites are designed to prevent cross-contamination.

EQUIPMENT

Equipment used in the manufacture of Valsartan, USP includes but is not limited to: reactors, centrifuges, filter presses, and a double cone rotary dryer. Equipment is assigned a unique equipment identification number. No deficiencies were noted regarding equipment size or location.

The firm does not use food grade coolants in jacketed reactors used in the firm's workshops (**FDA Observation 8**). The firm does not have validated cleaning procedures (**FDA 483 Observation 2e**). Cleaning procedures do not contain sufficient details to ensure cleaning procedures are consistently followed (**FDA 483 Observation 5**). Equipment is not always appropriately designed for its intended use, cleaning, and maintenance (**FDA Observation 6a, 6b, and 6c**). Preventive maintenance schedules are not always adequate (**FDA483 Observation 7a, 7b, and 7c**).

MATERIALS MANAGEMENT

Components, containers and closures are identified. Incoming components, containers and closures are quarantined until sampled, tested, approved and released for use. At least one specific identity test is conducted for each component. Containers and closures are visually examined. Components, containers and closures are used on a FIFO (First-in-First-out) basis. Partial coverage was given to the Materials Management System.

Sampling procedures do not always ensure samples are representative (**FDA 483 Observation 9**). The firm has a written procedure for vendor qualification Management System of API Material Supplier SMP-015.08 effective October 1, 2017. Management System of API Material Supplier is silent regarding the allowable difference in results between the manufacturer's CoA (Certificate of Analysis) reported test results and the firm's test results as part of verification of the reliability of the manufacturer's CoA. I reviewed the firms audit report for the manufacture of starting material, Br-OTBN. Nothing remarkable was noted.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

PRODUCTION

No deficiencies were noted regarding charging in of components, manufacturing formulation, identification of equipment with contents, calculation and documentation of yield, and equipment cleaning and use logs. The firm started manufacturing Valsartan, USP for validation of the firm's new optimized process for Valsartan July 23, 2018. Manufacturing of the first Valsartan batch was not completed prior to the end of this inspection. The firm did not have an approved validation protocol prior to July 23, 2018.

The firm's change control system to evaluate changes that may affect the production and control of intermediates or APIs is not adequate (**FDA 483 Observation 1ai, 1aii, 1bi, and 1bii**). Validation of manufacturing processes is not always adequate (**FDA Observation 2a, 2bi, 2bii, 2biii, 2c and 2d**). Production deviations are not always adequately reported and evaluated and critical deviations are not always investigated (**FDA 483 Observation 11a and 11b**).

The firm has a written procedure Deviation Investigation Management System SMP-017.05 effective January 1, 2018. Deviation investigations are not always thoroughly investigated and documented [**Exhibit 121**] (**FDA Observation 3c**). On-going deviation investigation DCE-18001 was initiated June 6, 2018 [**Exhibit 113**]. The deviation investigation was initiated for suspected genotoxic impurity in Valsartan. On June 6, 2018 Novartis notified the firm test results from a third-party laboratory found a small peak after the Toluene peak during Residual Solvent testing using a GC-MS test method. Dr. Li stated retrospectively the firm knew a very tiny peak (like noise) would elute after Toluene in GC-FID testing. Novartis notified the firm Novartis suspected the peak was NDMA (N-Nitrosodimethylamine). **Exhibit 165** includes chromatographs from GC-FID testing from three batches manufactured using Process II (TEA) manufacturing process prior to changing to Process II (DMF) and three batches manufactured as part of process validation for the new process. The peak location and peak size is consistent both before the change and after the change. **Exhibit 177** is the CoAs (Certificates of Analysis) for the six Valsartan batches manufactured before and after the change.

Mr. Du stated Novartis has the largest market share in China. Mr. Du stated Valsartan API manufactured using Process II (TEA) was approved for sale in China in June 2012. Mr. Du stated finished dosage Valsartan was approved for sale in China May 23, 2018 [**Exhibit 163**]. Valsartan API manufactured using Process II (DMF) was approved for sale in China in May 2017 [**Exhibit 113 page 21**].

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

DCE-18001 is classified as a major deviation. As part of the deviation investigation the firm prepared a Deviation Investigation Report dated July 20, 2018 [Exhibit 113 pages 12-120]. On June 9, 2018, the firm used a qualitative GC-MS method to confirm the structure of the unknown peak is NDMA. The firm is in the process of developing a validated quantitative GC-MS method for testing NDMA concentrations [Exhibit 164]. The firm hypothesizes the presence of trace amounts of NDMA in the final Valsartan API requires the convergence of the following three factors: 1) use of DMF in the tetrazole formation step, 2) quenching of azide using nitrous acid, and 3) quenching takes place in the presence of the product [Exhibit 113 page 20].

The firm has had three different manufacturing processes for the manufacture of Valsartan. Mr. Du stated Process I was never commercialized. Valsartan manufactured from Process II [(TEA) Triethylamine Hydrochloride catalyst and Toluene solvent)] was assigned the following product codes: C5069, C5354, and D5195. Valsartan manufactured from Process II [(DMF) Dimethyl Formamide solvent and Zinc Chloride catalyst] was assigned the following product codes: C5355 (manufactured in Workshop 2), C5523 (manufactured in Workshop 13) and D5191 (manufactured in Workshop W02). Product codes containing the letter “D” indicate the product is manufactured in a workshop in the West Zone. Product codes containing the letter “C” indicate the product is manufactured in a workshop in the East Zone.

The firm tested three Valsartan batches manufactured using Process II (TEA): C5354-11-001, C5354-11-002, and C5354-11-003 using an un-validated GC-MS method and detected no NDMA (LOQ about 1 ppm). The firm hypothesizes other sartan drugs will not have NDMA because the three factors that must converge do not exist in other sartan drugs manufactured at the firm. The firm tested three lots from 6 of the 7 sartan APIs the firm manufactures and did not detect NDMA [Exhibit 113 page 34].

On August 1, 2018, I asked Mr. Du if the firm tested Valsartan manufactured using Process II (TEA) processing method for the Chinese market for NDMA. On August 2, 2018, Mr. Du stated the firm tested Valsartan manufactured using Process II (TEA) processing method for the Chinese market for NDMA on July 8, 2018 and obtained results for NDMA ranging from 11 ppm – 107 ppm with an average NDMA concentration of 56 ppm. I asked Mr. Du for a second time if the firm intended to re-evaluate the firm’s plan to continue with process validation for the optimized process now that NDMA was identified in Valsartan manufactured using Process II (TEA). Mr. Du stated no the firm intends to move forward with the new optimized process.

In the Deviation Investigation Report prepared July 20, 2018, the firm states the firm has developed and validated a sensitive GC-MS method that is suitable for testing the amounts of NDMA present in Valsartan batches [Exhibit 113 page 43]. On July 24, 2018, I asked for a copy of the firm’s GC-MS test method for testing NDMA [Exhibit 165]. Dr. Li stated the test method is not yet approved. The Deviation Investigation Report reports GC-MS test method validation completed July 31, 2018 (11 days after the report was prepared) [Exhibit 113 page 44]. Dr. Li stated the GC-MS headspace test

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

method was developed by the firm's on-site R&D (Research and Development) Laboratory. Dr. Li stated the Butyl-acetate impurity in Ethyl Acetate interferes with the ability to quantify NDMA. Dr. Li also stated if the Butyl-acetate co-elutes it gives a false positive.

I asked Dr. Li if the firm developed reaction equations for the potential side reactions as part of the firm's drug development for the new optimized process. Dr. Li stated no it isn't necessary. I asked Dr. Li if the firm will test for potential side reaction products and impurities and test the waste streams for potential side reaction products and impurities. Dr. Li stated no it isn't necessary.

The firm has master production batch records. Valsartan is manufactured in four different Workshops. There is a separate approved master production record for each Workshop. Mr. Dong stated if changes to the DMF (Drug Master File) require revision to the master production batch records the batch records are revised. I asked Mr. Dong if the DMF number is included in the master batch record. Mr. Dong stated no. I asked Mr. Dong how the firm can tell version of the DMF a master batch record is revised for. Mr. Dong stated he thought you could tell by the date a master batch record is approved. **Exhibit 168** lists the batch record version number for each Workshop associated with each DMF amendment. **Exhibit 169** lists the solvent used for each version of the DMF. **Exhibit 170** lists the solvent used in each Workshop.

I asked Ms. GE how the firm ensures the correct version of the batch record is issued for use. Ms. GE stated when the DMF is approved through approval of the customer's NDA (New Drug Application) the firm initiates change control to revise the master batch record. Ms. GE stated the revised batch record has a new version number.

(JDH) The firm has manufactured Valsartan in five workshops since 2008 using the processes referred to as the "triethylamine process" and "zinc chloride process". **Exhibit 41** lists the history of changes to the firm's Valsartan DMF 23491. As part of technical amendment 004, submitted in December 2013, the firm changed the manufacturing process which included changing the catalyst reagent to zinc chloride in step 4 (synthesis of crude valsartan) and adding solvents DMF (Dimethyl Formamide) and MTBE (Methyl Tert-butyl Ether) in steps 3 and 4. **Exhibit 29** includes a general comparison of solvents used in the earlier "triethylamine process" and the DMF/zinc chloride process.

There are five major steps in the manufacture of Valsartan:

- Step 1 – Synthesis of L-valine methyl ester hydrochloride
- Step 2 – Synthesis of N-[(2-cyano-biphenyl-4-yl)-methyl]-L-methyl valinate hydrochloride
- Step 3 – Synthesis of N-pentanoyl-N-[2'-cyano-biphenyl-4-yl)-methyl]-L-methyl valinate
- Step 4 – Synthesis of crude Valsartan
- Step 5 – Recrystallization

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

The manufacture of crude Valsartan (Step 4) in workshops 2, 13, and W02 was the focus of this inspection as they are currently used for manufacturing USDMF-specification Valsartan, which is intended for the U.S. market. I conducted walkthrough inspections of the crude Valsartan manufacturing areas in workshops 2, 13, and W02.

Workshop 4 has not been used since 2015 and workshop 12 was undergoing a complete renovation at the time of this inspection. All synthesis equipment had been removed from the facility and equipment throughout the clean area was being disassembled. The work began in June and is expected to be completed in the coming months. A change control describing the renovations to workshop 12 is included in **Exhibit 38**. The stated purpose of the change on the first page of the document translates as "To better satisfy the EHS (Environment, Health, Safety) requirement, to improve the operating environment of the workshop, to maintain and repair equipment, facilities, and workshop, to make the layout more rational."

A general process flow for the currently filed manufacturing process (zinc chloride process) for Valsartan in workshop 2, as an example, is included in **Exhibit 28**. **Exhibit 31** is a flow chart for the "optimized" process that will separate the quenching process believed to be a contributing factor to the formation of the NDMA impurity. This process is currently being validated by the firm. The first finished batches using this optimized manufacturing process were nearing completion at the time of the inspection. **Exhibit 39** shows the master batch record for the optimized crude Valsartan manufacturing process in workshop 2. **Exhibit 40** is a translated copy of this batch record.

The firm's evaluation and determination of the source of the formation of NDMA is explained in Deviation CDZ-18001 [**Exhibit 30, page 32**]. **Exhibit 46** provides details for specific manufacturing process steps in each of the workshops used to manufacture crude Valsartan with a summary of the firm's test results for the presence of NDMA for each workshop. Due to differences in the workshops the step numbers are slightly different from workshop to workshop. **Exhibits 32-34** include the crude Valsartan (step 4) batch records for the DMF/zinc chloride process in workshops 2, 13, and W02. **Exhibits 35-37** include English translations for each batch record.

LABORATORY/DESIGN OPERATIONS

Throughout the inspection, I interviewed employees and reviewed documentation associated with laboratory activities. Laboratory equipment includes but is not limited to: HPLCs, GCs, and UV-Vis Spectrophotometers. No deficiencies were noted regarding staffing, laboratory facilities, calibration, system suitability checks, or official standards. Sampling procedures are not always scientifically sound and/or they do not contain sufficient detail to ensure samples collected are representative (**FDA 483 Observation 9a, 9bi, 9bii, and 9c**).

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

The firm has a written procedure Recording and Reviewing for Laboratory Records QC-021.11 effective January 31, 2018. Data is reviewed by a second analyst in the laboratory who also conducts tests. Data is reviewed prior to batch release. Data is also reviewed again monthly. Prior to batch release data review includes a review of: audit trails, integration, repeated integration, manual integration, repeated sequence, and single injections.

The firm continues the practice of making additional injections for Assay results which are not within 2% of each other as shown in the injection history for HPLC injections [**Exhibit 185**]. I asked Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, why the firm is making repeat injections for Assay results within specification. Mr. Q. Li stated the Assay results are not very accurate and the firm wants to report the most accurate result. I asked Mr. Q. Li if the firm calculated the level of accuracy of the test method. Mr. Q. Li stated no. I asked Mr. Q. Li if the firm needed to develop and validate a new method given repeat injections can't improve the accuracy of the results or improve the accuracy of the test method. Mr. Q. Li understood my question, acknowledged my question, but did not provide a verbal response.

The manufacturing process for Valsartan is the same since December 2017 for all markets. **Exhibit 161** compares the product release specifications for Valsartan for each market. In-house test methods are used for Related Substances, Residual Solvents and Assay test methods.

The firm does not have an adequate procedure(s) for responding to and handling the identification of unknown peaks. The firm's written procedure API Chromatographic System Suitability Integrity Evaluation QC-013-6 effective September 20, 2017 states if abnormal peak report to QC Supervisor or Team Leader [**Exhibit 184 page 6 section 5.1.5.1.3**]. Mr. Yinhua Tang, Assistant Director QC, stated new peaks, ghost peaks, abnormal peaks, unspecified impurity peaks are only investigated if the peak is OOT (Out-of-Trend). I asked Mr. Tang if the firm has another written procedure(s) providing more details for how to handle any type abnormal, unknown, or unidentified peak. Mr. Tang stated no. I reviewed six OOS investigations for chromatography. The firm rejected the batch associated with two of the six OOS investigations and closed the OOS investigation without further investigation into the abnormal, unknown, or unidentified peak.

The test method for testing NDMA in Valsartan is not an approved and validated test method. I reviewed the Validation Protocol GC-MS Method (23 minutes) NDMA in Valsartan QRC-18027(P) effective July 12, 2018. I reviewed test method validation for: Validation USP Method and In-house Method Quality Comparison Research Report VLDQR-10-099 for Assay and Related Substance; Valsartan Residual Solvent Method Validation VLDC-09-048; Method Validation Report for Genotoxic Impurity Ethyl Carbamate Determination in Levetiracetam QRC-14040 (R); and Method Validation of Triple Quadrupole LC-MS Method for Ethyl Carbamate in Levetiracetam QRC-17021 (R) [**Exhibit 172**]. Validation of analytical test methods is not always adequate (**FDA 483 Observation 2d**). Mr. Wenquan Zhu, Assistant Director Quality Research, stated the Single Quadrupole LC-MS method for Ethyl Carbamate in Levetiracetam causes a false positive because

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

the concentration is too high to reach the desired sensitivity of the Single Quadrupole method. I asked Mr. Zhu if the firm has data to support the firm's hypothesis the Single Quadrupole method generates false positive results for Ethyl Carbamate in Levetiracetam. Mr. Zhu stated no. I asked Mr. Zhu if the firm spiked production samples with known concentrations of Ethyl Carbamate and calculated the recovery rate from the production samples to determine if the production samples of Levetiracetam included sample interference the test method should account for as part of validation of the Triple Quadrupole LC-MS test method [Exhibit 172]. Mr. Zhu stated no. I asked Mr. Zhu if the firm spiked production samples with known concentrations of Ethyl Carbamate and calculated the recovery rate from the production samples to determine if the production samples of Levetiracetam included sample interference the test method should account for as part of validation of the Single Quadrupole test method the firm states is responsible for false positive test results for Ethyl Carbamate. Mr. Zhu stated no.

The firm has a written procedure Laboratory OOS/OOT (Out-of-Specification/Out-of-Trend) Investigation Management System SMP-021.10 effective June 1, 2018. The firm does not always have scientifically sound reasons for invalidating OOS results (FDA 483 Observation 9a). Exhibit 160 is a list of OOS investigations for Valsartan from January 2016 to July 2018.

The firm does not visually examine reserve samples at least annually for evidence of product deterioration [Exhibit 183 photographs 2-3]. Exhibit 188 page 4 section 5.6.1 specifies unless otherwise specified out of 100 batches check the secondary packaging and label for integrity. I asked Mr. Yinhua Tang, Assistant Director QC, if the firm opens the reserve samples and checks the API for evidence of product deterioration. Mr. Tang stated no.

The firm does not have an adequate on-going stability study testing program to monitor the characteristics of APIs (FDA 483 Observation 10a and 10b). Due to time constraints, the microbiology laboratory(s) was not covered.

MANUFACTURING CODES

The firm's system for assigning manufacturing codes is described in the Establishment Inspection Report dated March 31, 2017. (JDH) Products with the "USP" specification are manufactured using what was described as a slightly different process and per firm management, is not sold for the U.S. market. A list of customers for the USP-specification material is included in Exhibit 42. The firm identified the customers on this list known to be distributors with a check mark.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

COMPLAINTS

The firm has a written procedure Complaint Management Procedure SMP-011.08 effective October, 20, 2017 [Exhibit 174]. The firm follows the firm's deviation investigation procedure to investigate complaints [Exhibit 121]. The firm does not always ensure deviations are thoroughly investigated. (FDA 483 Observation 3).

The firm has a written procedure Returned Product Management Procedure SMP-012.02 effective October 30, 2013. The firm verifies the storage and shipment condition prior to accepting a return. The firm documents inspection of the containers and seals upon receipt. The firm does not always follow written procedures (FDA 483 Observation 3e). Return No. RD-17005 was assigned for Valsartan batch D5191-16-161 returned by Zhejiang Pharmaceutical Co., Ltd. finished dosage site for PSD (Particle Size Distribution) not meeting the finished dosage site's specification [Exhibit 178]. Primary packing was opened in six of the 24 returned drums. The firm sampled each of the six opened drums and performed identity testing on each drum sample, and tested a composite sample from the six opened drums against product release testing. All 24 drums of Valsartan batch D5191-16-161 were repackaged without reprocessing [Exhibit 179]. The batch number did not change after repackaging. Ms. GE stated the batch was sold to another customer who did not have a specification for PSD.

RECALL PROCEDURES

The firm has a written procedure Product Recall Management System SMP-013.07 effective October 20, 2017 [Exhibit 175]. The firm conducts a mock recall annually. On July 13, 2018 recall (RES number 80525) was initiated. The recalling firm Princeton Pharmaceutical Inc. (dba Solco Healthcare LLC) (FEI: 3009298353) is the [REDACTED] holder for [REDACTED] (Valsartan USP tablets 40/80/160/320 mg) and [REDACTED] (Valsartan and Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, 320 mg/25 mg). Zhejiang Huahai Pharmaceutical Co., Ltd. is the listed API manufacturer on both [REDACTED]. Mr. Jun Du, Executive Vice President, stated the firm has asked consignees to return all Valsartan batches manufactured using the Process II (Zinc Chloride catalyst and DMF solvent) manufacturing process. As of July 23, 2018, Mr. Jun Du stated the firm had not received returned Valsartan API batches in response to the recall.

Process I was a customer specific process. Mr. Du stated this process was never commercialized. Ms. Linda Lin, Director Regulatory Affairs headquarters, stated Process I ended February 2017. The firm then developed Valsartan Process II which did not use Zinc Chloride or DMF. The first version of Process II used the catalyst Triethylamine (TEA) and the solvent Toluene.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

I asked Mr. Du what the firm intends to do with the returned Valsartan batches. Mr. Du stated the FDA is asking to preapprove a protocol for reworking the returned batches of Valsartan. Mr. Du stated the firm is starting research on crude Valsartan to determine if recrystallization can remove the impurity. Mr. Du stated the firm does not want to rework the returned Valsartan batches. Mr. Min Li, PhD. (Bio-organic and Analytical Chemistry), Vice President of Analytical Operations Headquarters, stated it is not possible to remove the impurity by reprocessing returned Valsartan API batches. Mr. Du stated the firm has proposed a new optimized process and the firm wants to start manufacturing Valsartan from the new optimized process and does not want to reprocess returned batches of Valsartan API.

The firm has two manufacturing areas designated as the West Zone and the East Zone. **Exhibit 146** is an inventory list for Valsartan in the West Zone. **Exhibit 147** is an inventory list for Valsartan in the East Zone.

During the opening presentation on July 23, 2018, Mr. Du explained how the firm came to know Valsartan manufactured by the firm could contain the genotoxic impurity NDMA (N-Nitrosodimethylamine). Mr. Du stated Novartis placed an order with the firm for 45 Metric Tons of Valsartan. Mr. Du stated the order was fulfilled in multiple shipments [**Exhibit 144 and Exhibit 145**]. Novartis Purchase Order (PO) 4500653172 was fulfilled in 23 shipments. Mr. Du stated Novartis told the firm test results from a third-party laboratory indicated the presence of NDMA and asked the firm to confirm the third-party laboratory results. **Exhibit 166** includes test results Novartis obtained showing NDMA in Valsartan API samples. Mr. Du stated the third-party laboratory tested Valsartan using a GC-MS test method. Mr. Du stated Novartis tested Valsartan using a GC-FID test method and observed a small suspicious peak after the Toluene peak and that is why Novartis sent Valsartan samples to a third-party laboratory for further testing to identify the unknown peak.

Dr. Li stated Novartis told the firm the tiny peak Novartis observed after the Toluene peak seemed to be a genotoxic impurity and asked the firm to confirm. The firm tested Valsartan using a qualitative GC-MS testing method and compared the peak to a reference standard and the reference library and the peak seemed to be a match for NDMA. Dr. Li stated the firm then developed a quantitative GC-MS test method.

I asked Dr. Li if the firm observed the small peak after the Toluene peak when the firm tested Valsartan using a GC-FID test method. Dr. Li stated the peak was below the sensitivity level of the test. Dr. Li further stated the peak area does not change when the concentration of NDMA changes. Dr. Li also stated it appears there are other substances in that area also. Dr. Li stated the peak area for the peak containing NDMA is typically less than 5 and it is not quantitative.

Mr. Du stated the firm has been holding teleconference calls with CDER (Center for Drug Evaluation and Research) staff involved with generic drugs, drug shortages, the review division for

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

Valsartan, and pharmaceutical toxicology. **Exhibit 149** includes communications with CDER. **Exhibit 150** is a communication timeline.

Dr. Li stated the impurity occurs only in Valsartan Process II when the solvent and reaction catalyst were changed. Dr. Li stated DMF (Dimethyl Formamide) has a low level of decomposition when the reaction temperature is about 130°C. Dr. Li further stated Nitrous Acid formed in situ reacts with trace amounts of dimethylamine in the reaction to form NDMA when the Valsartan product is present during the quenching step.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

QUALITY SYSTEM

OBSERVATION 1

The change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs) is not adequate. Specifically,

a) you do not always conduct a formal risk assessment for critical changes to evaluate the potential impact of proposed changes on the quality of intermediates or APIs. Critical Change Request PCRC-11025 was initiated November 27, 2011 and closed November 29, 2011, for the stated purpose of making changes to the Valsartan manufacturing process to reduce the current conversion rate (60% - 70%) of the known isomer impurity D-Valsartan in the final API and increase batch yields (current batch yield 400 - 500 Kg per batch).

i) you did not conduct and document a formal risk assessment for Change Request PCRC-11025 to evaluate the potential impact of proposed changes on the quality of the intermediates or the final API for this critical change to your validated manufacturing process prior to your quality unit approving the change.

ii) you hired an outside laboratory to conduct a small lab scale research project. Based on the results of a lab scale research project you initiated validation on a commercial scale to change your validated manufacturing process without conducting pilot scale or other small scale batches. Your Deputy Director of Manufacturing stated you have commercial experience and since you only changed the catalyst and the solvent there was no need to conduct pilot scale trial batches before instituting critical changes on a commercial scale.

You initiated validation on a commercial scale without conducting a formal risk assessment to evaluate the potential impact of changes to your validated manufacturing process on the quality of intermediates and APIs. You do not have a quality agreement with the outside laboratory you used to perform a lab scale research project requiring (prior to initiating testing and reporting results):

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

qualification of all instruments used to conduct tests; validation of all software used with qualified instruments to conduct tests; calibration of all applicable measurement devices against traceable standards prior to use; use of official standards as appropriate; if applicable, establishing system suitability prior to testing samples and processing data; and validation of all test methods used for testing.

b) you do not have an adequate change control system requiring scientific judgement to determine what additional testing and validation studies are appropriate to justify changes to a validated manufacturing process. You do not always have data to support approval of changes to validated processes.

i) You did not identify specific parameters and specify acceptance criteria for those parameters prior to implementing changes, as part of critical Change Request PCRC-11025, to use to evaluate if the implemented changes decreased the isomer conversion of D-Valsartan and increased the batch yield.

ii) Additional testing requirements associated with critical changes are not always based on sound scientific judgement. Change Request PCRC-11025 included changing both the catalyst and the solvent in your validated manufacturing process. Additional testing requirements associated with these changes were limited to three validation batches and a commitment to conduct additional testing on three batches a year.

c) you do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated process. You do not consistently classify changes. You do not always increase testing, validation, and the documentation required to justify changes to a validated process based on the classification of a proposed change. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 contradicts your internal Change Request PCRC-11025 which lists change control classification as critical change.

d) written change control procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit. Your quality unit does not always follow your written procedure for change control. Your written procedure Change Control System SMP-018.05 effective December 30, 2017 section 5.3.6 (3) specifies QA shall reject the change if the action cannot meet predetermined expectations. Critical Change Request PCRC-11025 did not include acceptance criteria with predetermined expectations. Valsartan Product Development Report-01 dated April 13, 2012 Table

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

8 includes D-Valsartan isomer impurity (specification $\leq 1.0\%$) from three batches manufactured according to the validated manufacturing process (results range from 0.46% - 0.57%) and Table 10 includes D-Valsartan isomer impurity from the three validation batches manufactured using a different catalyst and solvent (results range from 0.38% - 0.40%). The product development report is silent regarding evaluation of the ability of the implemented changes to reduce isomer conversion rates. Valsartan Product Development Report-01 did not compare the batch weights from batches manufactured immediately before the change to the validated manufacturing process and the first batches manufactured after implementing changes to the manufacturing process.

Supporting Evidence and Relevance:

1ai) Change Control Number PCRC-11025 [**Exhibit 101 page 2 No. 1**] was assigned to a request to make changes to the firm's validated Valsartan API manufacturing process (request date November 27, 2011) [**Exhibit 101 page 1 Change Type**]. The Change Request Form indicates the change request was closed November 29, 2011 [**Exhibit 101 page 5 Dept. Management Signature**]. The change request was identified by the firm as a critical change [**Exhibit 101 page 2 No. 3 Change Control Classification**].

The firm specified the reason for the change was the conversion rate of the isomer D-Valsartan is too high and the yield is low [**Exhibit 101 page 1 Reason**]. The firm further states the isomer conversion rate is 60%-70% and the yield is 400-500 Kg [**Exhibit 101 page 1 Current**]. The firm proposed changing the catalyst to Zinc Chloride [**Exhibit 101 page 1 Proposed**]. Change control related departments (Technical, Production, QC, Regulatory Affairs, Environmental Health and Safety, and QA) each evaluated the change by checking yes, no, or NA in response to short questions included in the Change Request Form [**Exhibit 101 pages 3-5 Section 3**]. I asked Ms. Jucai GE, QA Director, if the firm conducted a formal risk assessment to evaluate the potential impact of this critical change on the quality of the intermediate(s) and/or the final API prior to initiation of the change. Ms. GE stated yes. I asked Ms. GE if she was referring to the responses to the short questions included in the form. Ms. GE stated yes.

Valsartan Process II Zinc Chloride Process Change Summary is attached to the change request documentation [**Exhibit 101 pages 8-54**]. The attached Valsartan Process II Zinc Chloride Process Change Summary did not include a discussion of a formal risk assessment conducted prior to initiating process validation on a commercial scale for this critical change. I asked Ms. GE if the firm had additional documentation showing the firm's formal risk assessment for this critical change. No additional documentation was provided by the firm prior to the close of this inspection showing the firm conducted a formal risk assessment prior to initiating process validation on a commercial scale for this critical change other than responding yes, no, or NA to a series of short generic questions on the Change Request Form. The Change Request Form indicates QA then approved the

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

change without conducting an in-depth formal risk assessment [**Exhibit 101 page 5 Section 3 Explanation Section**].

The firm has a written procedure Quality Risk Management SMP-023.03 effective November 1, 2011 [**Exhibit 109**]. **Exhibit 9 Appendix 2: Application of Quality Risk Management page 30** states in the following table, the risk management tools recommended for each subject are enumerated. The tools enumerated in the table for process validation include: FMEA (Failure Mode Effects Analysis), process flow chart, and key analysis [**Exhibit 109 page 40 Appendix 2: Application of Quality Risk Management**]. Change Control Number PCRC-11025 did not include a Risk Assessment report or other documentation showing the firm used risk management tools: FEMA, process flow chart and/or key analysis [**Exhibit 101 page 2 No. 1**].

Iaii) The firm contracted an outside laboratory, Shanghai SynCores Technology Inc., to conduct a small lab scale research project. Based on the results of this small lab scale research project the firm initiated process validation on a commercial scale to change the firm's existing validated manufacturing process for the manufacture of Valsartan API [**Exhibit 105**]. I asked Ms. Linda Lin, Regulatory Affairs Director Headquarters, if the firm has a quality agreement with Shanghai SynCores Technology Inc. Ms. Lin stated the firm does not have a quality agreement with Shanghai SynCores Technology Inc. Ms. Lin stated the firm has a contract with Shanghai SynCores Technology Ltd. [**Exhibit 102**]. The contract does not include defined responsibilities for GMPs for each firm or specify the outside laboratory, prior to initiating testing and reporting results, should: qualify all instruments used to conduct testing, validate all software associated with qualified instruments used to conduct testing, use official standards as appropriate, calibrate all applicable measurement devices against traceable standards, establish system suitability prior to testing samples and processing data, and validate all test methods used for testing.

Research and Development Report of Valsartan (SC-1141) provided by Shanghai SynCores Technology Inc. dated January 20, 2011, specifies the synthesis process of crude Valsartan and the purification process including the solvent system need to be further optimized at the pilot scale [**Exhibit 105 page 23 Section 6 Future Improvement**]. I asked Mr. Peng Dong, Deputy Director East Zone, if the firm conducted pilot scale or other smaller scale trial batches prior to initiating commercial scale batches as part of validation for this critical change to the firm's validated manufacturing process. Mr. Dong stated because of the firm's commercial experience and because the firm was only changing the catalyst and the solvent the firm did not need to conduct pilot scale trial batches prior to instituting critical changes on a commercial scale. The firm approved the process change April 4, 2012 [**Exhibit 101 page 39**]. In the Change Request dated January 12, 2012, the firm identified the changes to the manufacturing method as a minor change to the manufacturing process [**Exhibit 101 page 51 Contents of the Change**].

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

1bi) Change Request PCRC-11025 [**Exhibit 101**] did not identify specific parameters the firm would use to evaluate the effectiveness of the requested change and the impact of the requested change on intermediate(s) and/or the final Valsartan API prior to implementing changes to the firm's validated manufacturing process for Valsartan API. Change Request PCRC-11025 did not specify acceptance criteria for specific parameters the firm would use to evaluate the effectiveness of the requested change and the impact of the requested change on intermediate(s) and/or the final Valsartan API prior to implementing changes to the firm's validated manufacturing process for Valsartan API. I asked Mr. Dong if the firm identified specific parameters with acceptance criteria the firm would use to evaluate the effectiveness of the requested change and the impact of the requested change on intermediate(s) and/or the final Valsartan API prior to implementing changes to the firm's validated manufacturing process for Valsartan API. Mr. Dong pointed to a table describing manufacturing operating ranges in Valsartan Process II Zinc Chloride Process Change Summary [**Exhibit 101 pages 14-16 Table 3.2**]. The table does not include acceptance criteria. I asked Mr. Dong if the firm established specific parameters with acceptance criteria which the firm used to evaluate if the isomer conversion was reduced and the yield increased. Mr. Dong again pointed to the same table.

Mr. Dong did not identify a specific parameter or parameters with acceptance criteria which indicate the effectiveness of the requested change in reducing isomer conversion and increasing yield. Mr. Jun Du, Executive Vice President, apologized and stated the change control should have stated the purpose of the change was to save money. Mr. Du further stated the cost reduction was so significant it is what made it possible for the firm to dominate the world market share.

Valsartan Process II Zinc Chloride Process Change Summary includes a comparison of the level of isomer D-Valsartan and total impurities for the three lab scale batches from the outside laboratory and three commercial scale batches manufactured by the firm [**Exhibit 101 pages 26 Table 6-1**]. The D-Valsartan (specification $\leq 1.0\%$) lab scale results ranged from 0.31% to 0.56% and the commercial scale results ranged from 0.47% to 0.56%. The commercial scale results are within the range of the lab scale results. The report does not include a comparison between the isomer results of the commercial scale validation batches with commercial batches manufactured prior to the change. The report does not compare the batch yield of the commercial scale validation batches with commercial batches manufactured prior to the change. The acceptable criteria listed in the validation protocol for Valsartan Process II Zinc Chloride Process is a list of process parameters with the critical process parameters highlighted [**Exhibit 103**]. The Validation Protocol for Valsartan Process II Zinc Chloride Process does not include acceptance criteria defining how much isomer D-Valsartan should be decreased or how much batch weight should be increased [**Exhibit 104**]. I asked Mr. Dong if the Validation Protocol for Valsartan Process II Zinc Chloride Process included acceptance criteria defining how much isomer D-Valsartan should be decreased or how much batch weight should be increased in relation to the firm's validated manufacturing process for Valsartan API. Mr. Dong stated no.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

1bii) The Validation Protocol for Valsartan Process II Zinc Chloride Process included additional testing for three validation batches in step 4 crude Valsartan for TLC (Thin Layer Chromatography) to determine the completeness of the reaction in the Tetrazole reaction and Saponification of the organic phase [Exhibit 104]. The validation protocol did not include additional testing of the Tetrazole reaction solution for side products and impurities, the waste organic phase for side products and impurities, the waste aqueous phase for side products and impurities, or the recovered solvents for impurities. I asked Dr. Li if the firm conducted additional testing of the Tetrazole reaction solution for side products and impurities, the waste organic phase for side products and impurities, the waste aqueous phase for side products and impurities, or the recovered solvents for impurities as part of drug development or process validation. Dr. Li stated they are not required to do that. The firm conducted residual solvent tests for DMF (Dimethyl Formamide) and MTBE (Methyl Tert-butyl Ether) as part of process validation and then committed to testing three batches a year after process validation [Exhibit 106].

1c) The firm has a written procedure Change Control System SMP-018.05 effective December 30, 2017, which applies to changes of validated, registered or commercialized products [Exhibit 107 page 2 Section 2.2]. Change Control System SMP-018.05 defines a major change as a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product [Exhibit 107 page 9 Section 5.2.1(1)]. Change Control System SMP-018.05 is silent regarding change classification critical. Change Control System SMP-018.05 does not describe how the firm determines the level of testing, validation and documentation required to justify changes to a validated manufacturing process. Change Control System SMP-018.05 specifies a feasibility report should be provided for a major change to identify the possible risk and propose remediation measures to reduce the corresponding risk [Exhibit 107 page 4 Section 4.1.1]. Change Request PCRC-11025 [Exhibit 101] did not include a feasibility report.

Change Control System SMP-018.05 specifies the change request must be discontinued if, upon completion, the process is unable to meet validation acceptance criteria required to support the change [Exhibit 107 page 8 Section 5.1.7]. Change Control System SMP-018.05 specifies QA shall reject the change if the action cannot meet predetermined expectations [Exhibit 107 page 14 Section 5.3.6(3)]. Change Request PCRC-11025 [Exhibit 101] is silent regarding the validation acceptance criteria required to support the change which demonstrates the change meets predetermined expectations.

The firm's Change Request Form for Change Control Number PCRC-11025 change control classification shows a box is checked for critical change [Exhibit 101 page 2 No. 2]. DMF Amendment to Valsartan USP (Process II), DMF# 23491 submitted December 10, 2013, identifies the changes in the technical amendment as minor changes for Drug Substance Manufacturing [Exhibit 108 page 1 Technical Amendment 1]. Change Control System SMP-018.05 defines a major change as a change that has a substantial potential to have an adverse effect on the identity,

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

strength, quality, purity, or potency of a drug product [Exhibit 107 page 9 Section 5.2.1(1)].
Change Control System SMP-018.05 is silent regarding change classification critical.

1d) Change Control System SMP-018.05 effective December 30, 2017, specifies QA shall reject the change if the action cannot meet predetermined expectations [Exhibit 107 page 14 Section 5.3.6(3)]. Change Control System SMP-018.05 specifies the change request must be discontinued if, upon completion, the process is unable to meet validation acceptance criteria required to support the change [Exhibit 107 page 8 Section 5.1.7]. Change Request Change Control Number PCRC-11025 [Exhibit 101] is silent regarding the validation acceptance criteria required to support the change which demonstrates the change meets predetermined expectations.

Valsartan Product Development Report dated April 13, 2012, [Exhibit 110 page 19 Table 8] includes D-Valsartan isomer impurity (specification $\leq 1.0\%$) from three batches manufactured according to the validated Triethylamine manufacturing process (results range from 0.46% - 0.57%) and Exhibit 110 page 21 Table 10 also includes D-Valsartan isomer impurity from the three validation batches manufactured using catalyst Zinc Chloride and solvent DMF (Dimethyl Formamide) (results range from 0.38% - 0.40%). Valsartan Product Development Report, dated April 13, 2012, is silent regarding evaluation of the ability of the implemented changes to reduce isomer conversion rates. Valsartan Product Development Report-01, dated April 13, 2012, did not compare the batch weights from batches manufactured immediately before the change to the validated Triethylamine manufacturing process and the first batches manufactured after implementing changes to the catalyst and solvent in the manufacturing process. QA approved Change Request Form for Change Control Number PCRC-11025 November 29, 2011, without requiring predetermined validation acceptance criteria to support the change which demonstrates the change meets predetermined expectations.

Discussion with Management:

Mr. Peng Dong, Deputy Director Chuannan East Zone, disagreed with the observation stating the firm conducted a risk assessment for change request PCRC-11025. Mr. Jun Du, Executive Vice President, stated the firm would not agree to make corrections until the firm determined if the observations are correct.

OBSERVATION 2

Validation of production processes, cleaning procedures, analytical methods, and in-process control test procedures are not always adequate. Specifically,

a) your manufacturing processes are not always capable of consistently producing final products meeting all product quality specifications. Deviation No. DCB18-17017 was initiated for OOS genotoxic impurity Ethyl Carbamate 0.29 ppm (specification ≤ 0.24 ppm) in Levetiracetam batch C5152-17-289M. Repeat test results included OOS results. As a corrective action you reprocessed

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

Levetiracetam batch C5152-17-289M by repeating the final purification step in your manufacturing process. You did not investigate corrective actions to your manufacturing process or to the manufacturing batch record to improve product consistency and manufacturing reproducibility, and to reduce the level of Ethyl Carbamate in the Levetiracetam intermediate crude. You did not develop a prevent action plan to prevent future OOS Ethyl Carbamate levels in the intermediate crude and final API.

Between December 16, 2016 and August 22, 2017, you initiated 17 OOS investigations for Ethyl Carbamate impurity in Levetiracetam. Of the 17 OOS investigations initiated for Ethyl Carbamate impurity in Levetiracetam you attributed 13 OOS results to lab related errors, 5 OOS results to production errors, and 2 OOS results to a combination of lab and production errors. You reprocessed all 17 Levetiracetam batches you investigated for OOS Ethyl Carbamate impurity.

b) written validation protocols are not always adequate.

i) Your Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 and Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) do not include the specific parameters with acceptance criteria to establish your manufacturing process is not only consistent and reproducible but able to fulfill the purpose for changing your validated manufacturing process.

ii) Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) specified the number of manufacturing batches to be manufactured as part of validation of your manufacturing process or discussed the number of validation batches to manufacture based on the complexity of the process or the magnitude of the process change.

iii) Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) included a sampling plan designed to demonstrate the consistency and reproducibility of your manufacturing process through batch uniformity data.

c) you do not always initiate investigations during process validation. Tadalafil process validation batch D2182-16-003 test results for Diastereo-isomer 2.22% (specification $\leq 3.0\%$) were OOT (Out-of-Trend) compared to the other five validation batches with Diastereo-isomer results ranging from 0.20% to 0.57%. You did not initiate an investigation to identify the CPP(s) (Critical Process Parameter), non-critical process parameter(s), raw material(s), or other influences which could impact Diastereo-isomer results in an effort to improve the quality and consistency of TD-2 (the product from the second synthesis step in the manufacture of Tadalafil).

d) you do not have sufficient data to demonstrate your in-house test methods, used for Assay and Related Substance testing of Valsartan, are at least equivalent to USP Monograph test methods.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

Valsartan USP Method and In-house Method Qualification Comparison Research Report VLDor-10-099 (R) version 2 effective August 29, 2014 does not include data showing you tested known concentrations of Valsartan and spiked Valsartan samples and then compared the results from your in-house test method with results from tested known concentrations of Valsartan and spiked Valsartan samples using the USP method to verify your in-house test results at least meet the acceptance criteria of the USP methods.

e) you do not have validated cleaning procedures. Cleaning procedures for reactors W02-203-1 and W02-204-3 in workshop W02, used in the manufacture of crude Valsartan, are not validated in that you do not have data to demonstrate the cleaning procedure is effective following manufacture of 100 consecutive batches. The most recent cleaning validation study, CVD-18015 (R), approved in July 2018, is based on 60 consecutive batches. The 2016 equipment use log for reactor W02-203-1 shows 97 consecutive batches were manufactured before cleaning. The 2016 equipment use log for reactor W02-204-3 shows 98 consecutive batches were manufactured before cleaning. Your Quality Assurance Director verbally confirmed no rinse samples were analyzed following either of these cleanings.

Supporting Evidence and Relevance:

Note: Observation 2bii should read "Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) specified the number of manufacturing batches to be manufactured based on the complexity of the process or the magnitude of the process change. Observation 2c should read ranging from 0.42% to 0.57%. Observation 2d should read VLDqr-10-099 (R).

2a) Deviation Number DCB18-17017 was initiated August 22, 2018 and closed October 24, 2017, for Levetiracetam batch number C5152-17-289M OOS (Out-of-Specification) genotoxic impurity Ethyl Carbamate 0.29 ppm (specification < 0.24 ppm) [Exhibit 111]. The Deviation Investigation Report for Valsartan attached to Deviation Number DCB18-17017 summary table lists 17 OOS investigations involving 23 batches of Levetiracetam between January 22, 2016 and June 29, 2017 [Exhibit 111 pages 13-14 Section 3.1.1]. A review of lab investigations show repeat tests include OOS results in 6 of the 23 batches including Levetiracetam batch number C5152-17-289M [Exhibit 111 pages 15-16 Section 2]. The Deviation Investigation Report states the results of the second analyst (0.21 ppm) are significantly different from the original result (0.29 ppm) and identifies a suspected root cause of residual Levetiracetam and Ethyl Carbamate in the system [Exhibit 111 pages 17]. The Deviation Investigation Report further states between December 16, 2016 and August 22, 2017, three OOS results were due to lab error caused by the accuracy and sensitivity limit of a Single Quadrupole LC-MS system which generates false positive results [Exhibit 111 pages 17]. Deviation Investigation Report specifies to reprocess Levetiracetam batch number C5152-17-289M as the corrective action [Exhibit 111 pages 26 Section 7].

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

I asked Dr. Li if the firm reprocessed all 17 batches of Levetiracetam with OOS results for Ethyl Carbamate. Dr. Li stated yes. Dr. Li further stated 3 of the 17 OOS results were attributed to instrument error, 5 of the 17 OOS results were attributed to production error, 10 of the 17 OOS results were attributed to lab error, and 2 of the 17 OOS results were attributed to both lab and production errors. I asked Dr. Li if the firm tests the concentration of Ethyl Carbamate from ROS (Root of Synthesis) step 3 of refined Levetiracetam before continuing in the next manufacturing step for crystallization (final purification step). Dr. Li stated no.

I asked Ms. GE if the firm investigated corrective actions to the firm's manufacturing process or to the manufacturing batch record to improve product consistency and manufacturing reproducibility, and to reduce the level of Ethyl Carbamate in the Levetiracetam intermediate crude. Ms. GE stated no. I asked Ms. GE if the firm developed a preventive action plan to prevent future OOS Ethyl Carbamate levels in intermediate crude Levetiracetam and the final Levetiracetam API. Ms. GE stated no.

2bi) Change Control Number PCRC-11025 was requested November 27, 2011 to make changes to the firm's validated manufacturing process for Valsartan because the conversion rate of the isomer D-Valsartan is too high and the yield is low [**Exhibit 101 page 1 Reason**]. Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 [**Exhibit 104**] does not include specific process parameters with acceptance criteria to establish the manufacturing process after the change fulfills the purpose of the change to the firm's validated manufacturing process. Change Control Number PCRC-18021 was requested July 12, 2018 to make changes to the firm's validated manufacturing process for Valsartan because the original crude step can generate NDMA [**Exhibit 116 page 1 Reason**]. Change Control Number PCRC-18021 states Dimethylamine and Sodium Nitrite under acidic conditions can generate NDMA but these conditions do not exist in the proposed process change so NDMA will not generate [**Exhibit 116 page 1 Technical Information**]. Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112**] does not include specific process parameters with acceptance criteria to establish the manufacturing process after the change fulfills the purpose of the change to the firm's validated manufacturing process.

Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112 page 5 Section 8.3.1**] is not approved. The firm began manufacturing the first validation batch on or before the start of this inspection. I asked Mr. Dong if the Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) is approved. Mr. Dong stated the protocol is not completed or approved yet. The Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) I reviewed did not include acceptance criteria for NDMA in the intermediate crude and/or the final API. I asked Mr. Dong why Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) did not include acceptance criteria for NDMA in the intermediate crude and/or the final API. Mr. Dong stated the firm did not have a validated test method at the time the protocol was

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

written and due to the rushed nature of the circumstance the firm did not have time to complete the protocol prior to implementation of process validation. I asked Mr. Dong if the firm could have calculated the Threshold of Toxicological Concern (TTC) and used the calculated TTC as the specification for NDMA. Mr. Dong understood my question, acknowledged my question, but did not provide a verbal response. Prior to providing a copy of Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) the firm entered a specification for NDMA in the final API. I asked the firm to provide a copy of the specification I reviewed which did not include a specification for NDMA. A copy of the Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) I reviewed which did not include a specification for NDMA was not provided prior to the close of this inspection. Ms. GE stated the copy I reviewed included a specification for NDMA.

Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) specifies the firm will use full scan GC-MS mode to test the three validation batches to make sure no new genotoxic impurity is generated by the optimized process [**Exhibit 112 page 12 Section 2**]. I asked Mr. Dong if the firm plans to continue this test after the three process validation batches. Mr. Dong stated no. Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) includes a Summary for Process Optimization for the Valsartan Crude Step which concludes the process is validated by lab scale tests [**Exhibit 112 page 30 Section Conclusion**]. I asked Mr. Dong if the firm has an acceptance criteria for NDMA in the crude wet Valsartan cake produced from chemical synthesis step 4 and/or the final API. Mr. Dong stated no. Mr. Dong also stated the firm does not have a test method to test the concentration of NDMA in the wet cake.

I asked Mr. Du how the firm can conclude the process is validated when: the firm does not have an approved validation protocol, the firm has not completed manufacture of the first process validation batch, the firm did not test the concentration of NDMA in the wet cake to establish the level of NDMA that can be removed in the next crystallization step in the manufacturing process, and the firm does not have an approved validated test method for measuring the concentration of NDMA in the wet cake or the final Valsartan API. Mr. Du stated you are right we shouldn't have put that in the summary report.

2bii) Validation Protocol for Zinc Chloride Process Valsartan Workshop II CMVP-11-075 [**Exhibit 104**] states the firm will manufacture three batches, the protocol does not include a discussion of the number of process validation batches to manufacture based on the complexity of the process or the magnitude of the change. Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112**] states the firm will manufacture three batches, the protocol does not include a discussion of the number of process validation batches to manufacture based on the complexity of the process or the magnitude of the change. I asked Mr. Dong if the firm discussed the number of batches to manufacture based on the complexity of the process or the magnitude of the change. Mr. Dong stated there was no need to manufacture more than three batches based on the firm's

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

experience and knowledge. I asked Mr. Dong if the firm had a discussion regarding the number of batches required for process validation for this change. Mr. Dong stated no.

2biii) Validation Protocol for Zinc Chloride Process Valsartan Workshop II CMVP-11-075 [**Exhibit 104**] does not include a sampling plan designed to establish batch uniformity. Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112**] does not include a sampling plan designed to establish batch uniformity. I asked Ms. GE if either Validation Protocol for Zinc Chloride Process Valsartan Workshop II CMVP-11-075 or Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) included a sampling plan designed to establish batch uniformity. Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, stated it is not necessary to include a sampling plan designed to establish batch uniformity for those validation protocols because the Process Re-Validation Protocol for Valsartan PVC-17036 (P) from 2017 included a sampling plan designed to establish batch uniformity.

2c) Tadalafil process validation batch D2182-16-003 results for Diastereo-isomer 2.22% (specification < 3.0%) is OOT (Out-of-Trend) compared to the other five validation batches with Diastereo-isomer results ranging from 0.42% to 0.57% [**Exhibit 117**]. I asked Ms. GE if the firm initiated a deviation investigation to identify the CPP(s) (Critical Process Parameter), non-critical process parameter(s), raw material(s), or other influences which could impact Diastereo-isomer results; in an effort, to improve the quality and consistency of Tadalafil intermediate TD-2 (the product from the second chemical synthesis step in the manufacture of Tadalafil API). Ms. GE stated no.

2d) Valsartan USP Method and In-house Method Quality Comparison Research Report VLDqr-10-099 (R) for both Assay and Related Substance test methods did not include testing a known concentration of Valsartan and a series of spiked concentration Valsartan samples using the USP method and the firm's in-house test method to verify the firm's in-house test method meets the USP acceptance criteria [**Exhibit 118**]. I asked Mr. Wenquan Zhu, Assistant Director Quality Research Headquarters, if the firm tested a known concentration of Valsartan and a series of spiked concentration Valsartan samples using the USP method and the firm's in-house test method to establish the firm's in-house test method is at least equivalent to the USP method. Mr. Zhu stated no. Dr. Li stated the firm did better than that because the firm validated the USP test method. I asked Dr. Li if the USP test method is already a validated test method. Dr. Li stated yes. I asked Dr. Li how validating an already validated test method establishes the firm's in-house test method is at least equivalent to the USP method. Dr. Li understood the question, acknowledged the question, but did not provide a verbal response.

2e) (JDH) Reactor W02-203-1 is one of the reactors that may be used in crude Valsartan manufacturing steps 5.1 through 5.5 [**Exhibit 37**]. Reactor W02-204-3 is one of the reactors that

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

may be used for crude Valsartan manufacturing steps 5.7 through 5.17 [Exhibit 37]. Exhibits 1-2 include cleaning procedures for reactors W02-203-1 and W02-204-3. Exhibit 3 photograph of the Cleaning Management Program for Valsartan SOP showing that the procedure indicates the routine cleaning of the reactors should be conducted after 100 consecutive batches. Exhibit 4 photographs 1-2 show the cover page and approval page of validation report CVD-18015 (R). Exhibit 5 photograph shows the equipment use log for reactor W02-203-1 cleaning after 60 batches. Exhibit 4 photograph 3 shows cleaning identification number W02-203-1-18003 corresponds to the cleaning listed in the validation report used to support the cleaning validation. Ms. GE, QA Director, stated cleaning validation is ongoing and that only 60 consecutive batches were completed before the firm changed the manufacturing process to separate the quenching step. I informed Ms. GE based on the available data, the firm's cleaning validation does not support cleaning after up to 100 consecutive batches as the firm currently has data to support cleaning after 60 consecutive batches. The firm bases their cleaning procedures and cleaning validation based on a maximum carryover of 100 ppm of Valsartan from batch to batch. (CAC) The firm does not test for Valsartan as part of cleaning validation. The firm tests rinse and swab samples for TOC (Total Organic Carbon) as part of cleaning validation.

(JDH) In addition, I reviewed the equipment use logs for these two reactors dating back to 2016 and found that reactor W02-203-1 had up to 97 consecutive batches manufactured prior to cleaning [Exhibit 6] and reactor W02-204-3 had 98 consecutive batches manufactured prior to cleaning [Exhibit 7]. Ms. GE stated they did not collect and test rinse or swab samples as part of the cleanings identified in the equipment use logs. The firm does not have data that quantifies residuals in these reactors or demonstrates the effectiveness of the cleaning procedures for consecutive batch runs approaching 100 batches as stated in the firm's cleaning procedure.

Discussion with Management:

Ms. Jucai GE, Director QA, disagreed with the observation stating the firm determined the OOS results were due to false positive results. Ms. GE further stated it was not necessary to include a sampling plan to evaluate batch uniformity because the firm included a sampling plan to determine batch uniformity as part of the validation process for Valsartan TEA process using the catalyst Zinc Chloride.

Mr. Dong disagreed with the observation stating the firm included a target weight range as an acceptance criteria.

Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, disagreed with the observation stating it is not necessary to test known concentrations for the Assay using both the in-house method and the USP method because the acceptance range is so large.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI:

3003885745

EI Start:

07/23/2018

EI End:

08/03/2018

OBSERVATION 3

The system for managing quality to ensure confidence that the API will meet its intended specifications for quality and purity is not adequate in that your quality unit lacks written procedures and the authority and responsibility to ensure all critical deviations are thoroughly investigated. Specifically,

a) you release finished APIs manufactured from crude intermediates with OOS levels of genotoxic impurities without conducting a thorough investigation. Deviation No. DCB18-17025 initiated December 13, 2017 and closed April 16, 2018 was initiated for OOS Ethyl Carbamate impurity 0.32 ppm (specification ≤ 0.24 ppm) in Levetiracetam batch C5152-17-432. You identified the root cause as an equipment failure which impacted intermediate crude Levetiracetam batch C2447-17-411 during distillation. You reprocessed Levetiracetam batch C5152-17-432. Intermediate crude Levetiracetam batch C2447-17-411 was also used in Levetiracetam API final batch C5152-17-433. You did not reprocess batch C5152-17-433 made from OOS intermediate crude Levetiracetam batch C2447-17-411. You did not open an investigation, or conduct additional testing on batch C5152-17-433. Your QA Director stated batch C5152-17-433 met the product release specification for Related Substance Ethyl Carbamate.

b) major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for Valsartan batches D5191-17-023 and D5191-17-024 with OOS results for a single unknown impurity (specification $\leq 0.10\%$). You confirmed OOS results for Valsartan batches D5191-17-023 single unknown impurity 0.33%, and D5191-17-024 single unknown impurity 0.38%.

i) you did not identify a root cause for the single unknown impurity results in batches D5191-17-023 and D5191-17-024. You stated the root cause was probably due to occasional fluctuation in your manufacturing process. You did not attempt to identify this single unknown impurity. You did not attempt to identify the source of fluctuations in your manufacturing process for Valsartan.

ii) you did not develop an adequate Corrective Action and Preventive Action (CAPA) plan. The CAPA you listed on Deviation Investigation Report Form for Deviation DDW02-17003 included: discarding both batches, and following-up on the next 30 batches to see if a similar issue occurs. You did not review your manufacturing process and manufacturing batch records to determine if your manufacturing process and manufacturing batch records could be revised to reduce process variation. You did not interview employees to determine if employees consistently and reproducibly follow your manufacturing instructions.

iii) you did not conduct a thorough risk assessment. Your risk assessment consisted of answering 26 generic questions: yes, no, or NA (Not Applicable). Deviation DDW02-17003 investigation did not include documentation showing a more thorough risk assessment was conducted by your risk management team. Your written procedure for Quality Risk Management SMP-023.03 effective November 1, 2017 section 7.1.3 specifies a risk management team should be established when solving major risk issues, and section 7.1.5 of the same procedure specifies to select different tools according to the risk category. Quality Risk Management SMP-023.03 section 8.3 specifies all activities should be defined and documented. Quality Risk Management SMP-023.03 does not

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

specify which risk management methods and tools to use in association with specific deviation categories.

c) you do not always thoroughly document investigations. your written procedure Deviation Investigation Management System SMP-017.05 effective January 1, 2018 section 6.4.2 specifies the investigation should be well documented including the quality risk assessment (the same specification as included in version SMP-17.04 effective May 30, 2016). Deviation Investigation Management System SMP-017.05 like SMP-017.04 does not specify which risk management methods and tools to use in association with specific deviation categories.

d) you do not always thoroughly investigate deviations before closing the deviation. Deviation DCB02-17002 was initiated October 10, 2017 and closed February 1, 2018 for single unknown impurity (specification <0.50%) Valsartan intermediate condensate HCl batches C20213-17-339 (0.56%) and C20214-17-340 (0.56%). The Deviation Investigation Report states unspecified impurity at RRT (Relative Retention Time) 3.2 minutes is an in-process impurity observed in other batches but at levels not more than 0.10%. You did not identify a root cause. Your corrective action plan included: use LC-MS to identify the impurity, conduct further investigations once the impurity is identified, and conduct a lab trial study to determine if reprocessing removes the impurity. You did not develop a preventive action plan. You did not identify the single unknown impurity. You reprocessed Valsartan intermediate condensate HCl batches C20213-17-339 and C20214-17-340 and assigned the reprocessed batches final API batch numbers C5355-18-023M and C5355-17-024M. You then closed the investigation without identifying the single unknown impurity.

e) you do not always follow your written procedures. Returned Products Management Procedure SMP-012.02 effective October 30, 2013 defines a quality-related issue as any non-compliance to physical, chemical or microbiological feature. You classified Return No. RC-18006 as not quality related for Valsartan batches C5069-15-034MM and C5069-15-037MMM returned for not complying with customer PSD specifications, a physical feature. The Treatment Record section and closure date on Return No. RC-18006 were left blank.

Supporting Evidence and Relevance:

3a) Major deviation Deviation No. DCB18-17025 initiated December 13, 2017 and closed April 16, 2018, was initiated for OOS genotoxic impurity Ethyl Carbamate 0.32 ppm (specification ≤ 0.24 ppm) in Levetiracetam batch C5152-17-432 [Exhibit 119]. The Deviation Investigation Report states the root cause for the OOS results for Ethyl Carbamate in the final Levetiracetam API was equipment failure during the distillation of intermediate crude Levetiracetam batch C2447-17-411 (pipe flanges leaked during the distillation process and the insulation surrounding the pipe was removed during distillation) [Exhibit 119 page 25 Section 4]. I asked Mr. Dong if the firm

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

evaluated the firm's preventive maintenance schedule for the pipe flanges in the distillation unit. Mr. Dong stated no.

The firm reprocessed final Levetiracetam API batch C5152-17-432 which was made from intermediate crude Levetiracetam batch C2447-17-411 [**Exhibit 119 pages 25-26 Section 6**]. The firm did not reprocess final Levetiracetam API batch C5152-17-433 which was also made from intermediate crude Levetiracetam batch C2447-17-411 [**Exhibit 119 page 15 Section 3.4**]. I asked Mr. Dong if the firm tests intermediate crude Levetiracetam batches for Ethyl Carbamate impurity before releasing the intermediate crude Levetiracetam for the next step in the process. Mr. Dong stated no the firm tests three batches of intermediate crude Levetiracetam each year for Ethyl Carbamate impurity but not every batch. I asked Mr. Dong if the firm reprocessed final Levetiracetam API batch C5152-17-433. Mr. Dong stated no it was not necessary to reprocess final Levetiracetam API batch C5152-17-433 because the next step is a purification step which removes the impurity and the batch met product release specifications. I asked Mr. Dong if the purification step removed the impurity in final Levetiracetam API batch C5152-17-432. Mr. Dong acknowledged the question, understood the question, but did not provide a verbal response.

I asked Ms. GE if the firm opened an investigation for final Levetiracetam API batch C5152-17-433 made from intermediate crude Levetiracetam batch C2447-17-411 which led to OOS Ethyl Carbamate impurity 0.32 ppm in Levetiracetam batch C5152-17-432. Ms. GE stated no. Ms. GE further stated it was not necessary to open an investigation because final Levetiracetam API batch C5152-17-433 met final product release specifications for Related Substance Ethyl Carbamate. I asked Ms. GE if the firm conducted any additional testing on final Levetiracetam API batch C5152-17-433 prior to approving and releasing the batch. Ms. GE stated no.

3bi) Major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for Valsartan batches D5191-17-023 (single unknown impurity 0.33%) and D5191-17-024 (single unknown impurity 0.38%) with OOS results for a single unknown impurity (specification $\leq 0.10\%$) [**Exhibit 120**]. The firm confirmed OOS results for Valsartan batches D5191-17-023 single unknown impurity 0.33%, and D5191-17-024 single unknown impurity 0.38% [**Exhibit 120 page 1 Description**]. The firm stated the root cause was probably due to occasional fluctuation in production [**Exhibit 120 page 5 Conclusion**].

I asked Mr. Dong if the firm attempted to identify the single unknown impurity. Mr. Dong stated no. I asked Mr. Jinyi Li, QA Manager West Zone, if the firm identified the single unknown impurity. Mr. J. Li stated no. Mr. J. Li further stated historically it is a small peak so the firm thinks it is an isolated case. Dr. Li stated it is not necessary to identify a single unknown impurity at this level.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

The firm discarded both batches [**Exhibit 120 page 6 Section 4 CAPA**] without attempting to identify the single unknown impurity. I asked Ms. GE if the firm conducted a risk assessment in addition to answering 26 short generic questions on the Deviation Investigation Report Form: yes, no, or NA. Ms. GE stated no. I asked Ms. GE who decided not to further investigate the single unknown impurity. Ms. GE stated it was a joint decision made by Technology, QC and QA.

Deviation DDW02-17003 did not include investigation of the raw material used in the manufacture of Valsartan to review the quality of the raw materials or identify any OOT raw material test results. Deviation DDW02-17003 did not include extending the investigation to other batches using the same raw materials. Ethyl Acetate lot D1111-17-029 was used in other lots. I asked Mr. Dong if the firm investigated other batches of Valsartan using Ethyl Acetate lot D1111-17-029. Mr. Dong stated no. I asked Mr. Dong if the firm retested Ethyl Acetate lot D1111-17-029 for potential impurities. Mr. Dong stated no. I asked Mr. Dong if the firm identified any other OOS investigations where Ethyl Acetate lot D1111-17-029 was used. Mr. Dong stated he did not know. I asked Ms. GE if the firm identified any other OOS investigations where Ethyl Acetate lot D1111-17-029 was used. Ms. GE stated she didn't think so. Ms. GE did not provide additional information regarding the use of Ethyl Acetate lot D1111-17-029 in other lots. Ms. GE stated the firm has a paper system and it takes time to look through every document to try to identify if Ethyl Acetate lot D1111-17-029 was used in the manufacture of other final APIs involved in a deviation investigation.

I asked Mr. Dong if the firm attempted to identify the source of fluctuation in the firm's manufacturing process for Valsartan. Mr. Dong stated no, the firm reviewed the batch record and did not identify any abnormalities. The firm identified a set of possible factors that may impact the size of the single unknown impurity. I asked Mr. Dong if the firm proved or disproved the firm's hypothesis regarding the possible factors that may impact the size of the single unknown impurity. Mr. Dong stated no. I asked Mr. Dong if the firm performed any additional cleaning in response to this investigation. Mr. Dong stated no.

3bii) Deviation DDW02-17003 identified the firm's Corrective Action and Preventive Action (CAPA) plan as: discarding both batches, and following-up on the next 30 batches to see if a similar issue occurs [**Exhibit 120 page 6 Section 4 CAPA**]. I asked Mr. Dong if the firm reviewed the Valsartan manufacturing process and manufacturing batch records to determine if the Valsartan manufacturing process and/or manufacturing batch records could be revised to reduce process variation. Mr. Dong stated no, it was not necessary because the firm reviewed the manufacturing batch records and did not find any anomalies. I asked Mr. Dong if the firm interviewed employees to determine if employees consistently and reproducibly follow the manufacturing instructions. Mr. Dong stated no, it was not necessary because the firm's review of the batch records did not identify any anomalies.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

3biii) Major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for Valsartan batches D5191-17-023 (single unknown impurity 0.33%) and D5191-17-024 (single unknown impurity 0.38%) with OOS results for a single unknown impurity (specification $\leq 0.10\%$) [Exhibit 120]. The firm discarded both batches [Exhibit 120 page 6 Section 4 CAPA] without attempting to identify the single unknown impurity. I asked Ms. GE if the conducted a risk assessment in addition to answering 26 short generic questions on the Deviation Investigation Report Form: yes, no, or NA. Ms. GE stated no. I asked Ms. GE who decided not to further investigate the single unknown impurity. Ms. GE stated it was a joint decision made by Technology, QC and QA.

Exhibit 109 Quality Risk Management SMP-023.03 effective November 11, 2011 **page 7 section 7.1.3** specifies a risk management team should be established when solving major risk issues, and **page 8 section 7.1.5** of the same procedure specifies to select different tools according to the risk category. **Exhibit 109** Quality Risk Management SMP-023.03 **page 14 section 8.3** specifies all activities should be defined and documented. Quality Risk Management SMP-023.03 does not specify which risk management methods and tools to use in association with specific deviation categories [Exhibit 109]. Deviation DDW02-17003 did not include documentation showing a more thorough risk assessment was conducted by the firm's risk management team [Exhibit 120].

3c) **Exhibit 121** Deviation Investigation Management System SMP-017.05 effective January 1, 2018 **page 12 section 6.4.2** specifies the investigation should be well documented including the quality risk assessment (the same specification as included in version SMP-17.04 effective May 30, 2016 [Exhibit 121 page 19 Summary of Changes from Previous Version]). Deviation Investigation Management System SMP-017.05 like SMP-017.04 does not specify which risk management methods and tools to use in association with specific deviation categories.

The firm's risk assessment for major Deviation DDW02-17003 consisted of firm employees answering 26 short generic questions on the Deviation Investigation Report Form: yes, no, or NA [Exhibit 120]. The firm conducted the same risk assessment for critical Change Control Number PCRC-11025 [Exhibit 101]. I reviewed 15 deviation investigations. In all 15 deviation investigations, the only documented risk assessment used by the firm were the answers to 26 short generic questions on the Deviation Investigation Report Form. The 15 deviation investigations did not include a discussion or evaluation of the appropriate risk assessment tool to use for the deviation based on the risk classification assigned to the deviation.

3d) Deviation DCB02-17002 was initiated October 10, 2017 and closed February 1, 2018 for single unknown impurity (specification $<0.50\%$) Valsartan intermediate condensate HCl batches C20213-17-339 (0.56%) and C20214-17-340 (0.56%) [Exhibit 122]. The Deviation Investigation Report states unspecified impurity at RRT (Relative Retention Time) 3.2 minutes is an in-process impurity observed in other batches but at levels not more than 0.10% [Exhibit 122 page 13]. The firm did

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

not identify a root cause [**Exhibit 122 page 13 section 3.1**]. The firm's corrective action plan included: use LC-MS to identify the impurity, conduct further investigations once the impurity is identified, and conduct a lab trial study to determine if reprocessing removes the impurity [**Exhibit 122 page 15 section 5**]. Deviation DCB02-17002 did not include a preventive action plan. I asked Ms. GE if the firm identified single unknown impurity in Valsartan intermediate condensate HCL batches C20213-17-339 and C20214-17-340. Ms. GE stated no. Ms. GE stated the firm intends to identify the single unknown impurity and develop a preventive action plan. I asked Ms. GE if the firm is conducting tests to identify the single unknown impurity. Ms. GE stated no. The firm reprocessed Valsartan intermediate condensate HCL batches C20213-17-339 and C20214-17-340 and assigned the reprocessed batches final API batch numbers C5355-18-023M and C5355-17-024M. The firm closed the investigation without identifying the single unknown impurity.

3e) Returned Products Management Procedure SMP-012.02 effective October 30, 2013 defines a quality-related issue as any non-compliance to physical, chemical or microbiological feature [**Exhibit 123**]. The firm classified Return No. RC-18006 as not quality related for Valsartan batches C5069-15-034MM and C5069-15-037MMM returned for not complying with customer PSD (Particle Size Distribution) specifications, a physical feature [**Exhibit 124 page 1 Classification**]. Sampling and Handling Evaluation of Returned Valsartan API states the quality is in compliance and PSD is a physical quality [**Exhibit 124 page 8 section Conclusion**]. The firm reprocessed and released the batches [**Exhibit 124 page 8 section Corrective & Preventive Actions Taken**].

I asked Ms. GE why the firm did not classify the return as quality related. Ms. GE stated the firm did not classify the return as quality related because the firm does not have a product release specification for PSD for Valsartan. I asked Ms. GE if particle size is a physical feature of the product. Ms. GE stated yes.

The Treatment Record section and closure date on Return No. RC-18006 were left blank [**Exhibit 124 page 3**]. There is no indication on the Treatment Record section and closure date on Return No. RC-18006 explaining why no information was recorded [**Exhibit 124 page 3**].

Discussion with Management:

Ms. GE disagreed with the observation stating the batch met the specifications for the European market so the batch was released. Ms. GE further stated the firm used a Fish Bone diagram to perform the risk assessment.

Mr. Du disagreed with the observation stating when you do not identify a root cause the only thing you can do is follow-up on the next 30 batches.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

OBSERVATION 4

The quality unit does not always fulfill the responsibilities of the quality unit to release or reject all APIs. Specifically, Valsartan batch C5069-15-037M (M designates the batch was micronized) did not meet your customer's specification for PSD (Particle Size Distribution D (0.9) 50 – 85 µm). The actual PSD values were not reported on the CoA (Certificate Analysis) for the batch. The quality unit did not complete a Product Release Form rejecting the batch for not meeting the customer's PSD specification with instructions for handling the batch.

Valsartan batch C5069-15-037M was micronized a second time and the batch number was changed to batch C5069-15-037MM (D (0.9) 84 µm). The quality unit completed a Product Release Form and identified the batch as released without further instructions for handling the batch. Yet Valsartan batch C5069-15-037MM was micronized a third time. After Valsartan batch C5069-15-037MM was micronized a third time PSD results were D (0.9) 71 µm. The quality unit completed a Product Release Form releasing the batch a second time.

Supporting Evidence and Relevance:

Valsartan batch C5069-15-037M (M designates the batch was micronized) did not meet the firm's customer's specification for PSD (Particle Size Distribution D (0.9) 50 – 85 µm). Valsartan batch C5069-15-037MMM was returned, Return No. RC-18006, for not complying with customer PSD specifications [**Exhibit 124**]. The firm did not report the actual PSD value for D (0.9) on the CoA (Certificate Analysis) for batch C5069-15-037M [**Exhibit 125 page 23**]. The quality unit did not complete a Product Release Form rejecting batch C5069-15-037M for not meeting the customer's PSD specification with instructions for handling the batch [**Exhibit 125**].

Valsartan batch C5069-15-037M was micronized a second time and the batch number was changed to batch C5069-15-037MM (D (0.9) 84 µm) [**Exhibit 125 page 48**]. The quality unit completed a Product Release Form and identified the batch as released without further instructions for handling the batch [**Exhibit 125 page 50**]. The firm then micronized Valsartan batch C5069-15-037MM for a third time and assigned the micronized batch a new batch number, C5069-15-037MMM. After Valsartan batch C5069-15-037MM was micronized a third time PSD results were D (0.9) 71 µm [**Exhibit 126 page 26**]. The quality unit completed a Product Release Form releasing the batch a second time [**Exhibit 126 pages 28-29**].

Discussion with Management:

The firm disagreed with the observation. Ms. GE shook her head no and spoke in a loud voice. Mr. Du asked the translator not to translate the firm's disagreement.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

FACILITIES AND EQUIPMENT SYSTEM**OBSERVATION 5**

Cleaning procedures do not contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. Specifically, your cleaning procedures are inadequate in that three of the three reactors examined during the inspection contained visible residue or apparent foreign material. Reactor W02-102-1 contained apparent white particulate matter and what appeared to be a red-colored metallic particle. Reactor W02-102-2 contained apparent white residue. Reactor II-250 also contained apparent white residue along the length of the agitator shaft.

Supporting Evidence and Relevance:

(JDH) Reactors W02-102-1 and W02-102-2 are used in the esterification (step 1) in the Valsartan manufacturing process in workshop W02. Reactor II-250 is used in the acidification step in the manufacture of crude valsartan in workshop 2. **Exhibit 32 and Exhibit 28 pages 4-5** show the batch record steps 9.2 to 9.19. **Exhibit 9** includes the cleaning procedures for reactors W02-102-1 and W02-102-2. **Exhibit 8** includes the cleaning procedure for reactor II-250.

Exhibit 10 photograph shows the status tag for reactor W02-102-1 identifying the reactor as clean. **Exhibit 11 photograph** shows apparent white particles and a red-colored metallic like particle at the bottom of reactor W02-102-1. **Exhibit 12 photograph** shows the status tag for reactor W02-102-2 identifying the reactor as clean status. **Exhibit 12 photograph** shows an apparent white residue along the side of the reactor W02-102-2 near the bottom of the vessel.

Exhibit 14 photograph shows the equipment use logs for reactors W02-102-1 and W02-102-2 with the most recent cleaning documented on 07/02/2018 following manufacture of 22 consecutive batches. **Exhibit 15 photograph** shows the status tag for reactor II-250 identifying the reactor as clean. **Exhibit 16 photograph** shows apparent white residue along the length of the agitator shaft. I observed a production employee attach a cloth to a plastic pole to see if the white material could be wiped from the agitator. When the agitator was rubbed with a cloth, the white material was removed. Ms. GE was also present and observed this. Ms. GE agreed the substance appeared to be residue on the agitator shaft. **Exhibit 17 photograph** shows the equipment use log for reactor II-250 documenting the most recent cleaning on 06/29/2018 following manufacture of 1 batch.

The spotlights were on while I observed the interior of these reactors. I also used a flashlight provided by the firm to inspect the interior of the reactors. The residue and particulate matter were only visible when directly illuminated with the small flashlight beam as the lighting provided by the spotlights to the interior of the reactors was weak. The firm explained that the spotlight and flashlight are explosion-proof. However, it did not appear that the lighting is adequate to determine the visual cleanliness of the reactors.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

Discussion with Management:

The firm disagreed with the observation. Ms. GE shook her head no and spoke in a loud voice. Mr. Du asked the translator not to translate the firm's disagreement.

OBSERVATION 6

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, and maintenance. This is a repeat observation. Specifically,

a) you do not maintain equipment in a good state of repair. The end of the agitator shaft in reactor II-250 is not adequately repaired. The repaired area on the agitator shaft consists of three different colored unidentified materials: yellow, dull gray, and a silver metallic. Your Engineering Supervisor stated the dull gray material is the base layer of a liner repair material and the metallic-appearing material is the top layer of the same repair material. Only a small portion of the base layer covered the repaired area. The durability of the base layer in the absence of the top layer is unknown. The yellow material is unknown.

b) you do not have adequate lighting in glass lined reactors to inspect reactors after cleaning to ensure no visible residue remains.

c) you do not have an adequate heat sealing machine to seal final API aluminum bags. Heat sealing machine W05-811 does not have sufficient controls for pressure and time to ensure proper sealing. You do not conduct leak tests to check bag seals prior to final product approval and release.

Supporting Evidence and Relevance:

6a and 6b) (JDH) **Exhibit 18 photograph** showing the end of the agitator shaft in reactor II-250 with repairs. The dull gray material was identified as the base layer of the repair material. The shiny material, which didn't completely cover the base material, was described as the top layer. No one from the firm could identify the yellow material.

I asked if the top layer should completely cover the base layer. The firm's Supervisor of the Engineering Department explained that in a perfect world, the top layer should cover the base layer. I asked the Supervisor of the Engineering Department whether the repair was performed from within the vessel, or from the exterior of the vessel. The firm does not have a record describing how this work was performed. The firm does not have a written procedure describing how to repair the interior surfaces of the glass-lined reactors.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

Exhibit 19 photograph of the equipment use log for the reactor shows the repairs were made in February 2018. **Exhibit 20** includes an information sheet from the manufacturer of the repair material (Belzona) that briefly describes the use and testing of the manufacturer's liner-repair agent. Step 3 and 4 of this document translates to the following: 3.) Use of Belzona; 1) Base layer: Use scraper to apply the Belzona base layer directly on the treated surface; 2) Top layer: After the first layer is applied, shall immediately apply the top layer according to the above table item (a); 4.) Test; 1) After each layer applied, shall conduct appearance test immediately; if any holes or any parts missed for coating, shall use scraper to apply the agent.; 2) Once the surface has been completely coated and hardened, a thorough appearance check shall be conducted to assure no holes or missed coating, as well as to confirm if any potential mechanical damage occurred.; 3) After hardening, shall use high voltage spark test to confirm the consistency of the coating. It is recommended to use 2500 volt direct current to conduct the spark test.

6c) (CAC) Heat sealing machine W05-811 used to seal final API aluminum bags in Workshop 5 does not have controls for pressure or time pressure and heat are applied the aluminum bag to form the seal to ensure proper sealing. Heat sealing machine W05-811 has a temperature controller. I asked Mr. Wang Peng, West Zone Plant Director, if heat sealing machine W05-811 has controls for pressure and time pressure and heat are applied to the aluminum bag to form the seal. Mr. Peng stated no. I asked Mr. Peng if the firm conducts leak tests to check bag seals prior to final product approval and release. Mr. Peng stated no. Mr. Peng further stated the firm visually examines the seals. Ms. GE stated the firm conducted leak tests as part of equipment qualification for heat seal machine W05-811. I did not cover the Packaging and Labeling System and did not inspect final API packaging.

Discussion with Management:

Ms. GE disagreed with the observation stating the heat sealing machine is qualified and the heat sealing machine does not have controls for pressure. Ms. GE further stated the firm conducted a leak test when the firm qualified the equipment.

OBSERVATION 7

Schedules and procedures for preventive maintenance of equipment are not adequate or do not exist. Specifically,

a) you do not have a written procedure describing how to conduct a spark test to verify the integrity of the interior surface of the glass-lined reactors in your manufacturing workshops. Glass-lined reactors are used in the manufacture of crude Valsartan in workshops 2, 13, and W02.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

b) you do not have a written procedure describing how to perform repairs to the interior surfaces of glass-lined reactors. Repairs to interior surfaces of glass-lined reactors are made by your employees without written instructions for how to make those repairs.

c) you do not have a record showing a spark test was performed immediately following a repair to the glass-lining of the agitator shaft in reactor II-250. Reactor II-250 is used in the manufacture of crude Valsartan.

Supporting Evidence and Relevance:

7a, 7b, and 7c) (JDH) Ms. GE stated these procedures have not been developed and that no record documenting a spark test following repairs to the agitator was available.

Discussion with Management:

Ms. GE disagreed with the observation stating the material was not particulate and the material was not metallic.

OBSERVATION 8

Substances associated with the operation of equipment, such as lubricants, heating fluids or coolants are not always food grade lubricants and oils. Specifically, you use Ethylene Glycol in all of your jacketed glass-lined reactors in Workshop 5. You do not test Ethylene Glycol prior to release for use for Diethylene Glycol, a potential toxic contaminant. Rather than preventing potential finished API contamination from Diethylene Glycol by testing Ethylene Glycol for Diethylene Glycol prior to approval and release, your QA Director stated you periodically monitor your finished product APIs for Diethylene Glycol contamination.

Supporting Evidence and Relevance:

(CAC) Mr. Peng stated the firm uses Ethylene Glycol in the jacketed glass-lined reactors in Workshop 5. The firm's CoA for Ethylene Glycol does not include a test for DEG (Diethylene Glycol) [Exhibit 127 page 2]. I asked Ms. GE if the firm tests Ethylene Glycol prior to release for use for DEG, a potential toxic contaminant. Ms. GE stated no. Ms. GE stated the firm periodically monitors the finished product APIs for Diethylene Glycol contamination.

Discussion with Management:

Ms. GE disagreed with the observation stating the firm tests the finished API for DEG so there is not need to test Ethylene Glycol for DEG.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

LABORATORY SYSTEM**OBSERVATION 9**

Sampling plans, and test procedures are not always scientifically sound and appropriate to ensure raw materials, intermediates and APIs conform to established standards of quality.

a) you do not always have scientifically sound reasons for invalidating OOS results for lab related reasons. This is a repeat observation. Complaint No. CC-16008 received September 13, 2016 for Levetiracetam batches C5152-16-243 (0.25 ppm Ethyl Carbamate impurity) and C5152-16-254 (0.68 ppm Ethyl Carbamate impurity) failing to meet Ethyl Carbamate impurity specification ≤ 0.24 ppm identifies the complaint as a quality complaint for product quality attribute. Your Vice President of Analytical Operations stated a Single Quadrupole LC-MS is not as sensitive as a Triple Quadrupole LC-MS and sometimes it gives false positive results. Your customer tested Levetiracetam batches C5152-16-243 and C5152-16-254 using a Triple Quadrupole LC-MS. You sent samples of C5152-16-243 and C5152-16-254 to an outside laboratory to test using a Triple Quadrupole LC-MS. Your customer provided you with their LC-MS test method. The outside laboratory used a Triple Quadrupole LC-MS but did not follow the test method provided by your customer.

You do not have a quality agreement with this outside laboratory requiring all equipment used for testing is qualified, any software used with the instrument is validated, and the test method used is validated prior to reporting results. You used results from this outside laboratory for Levetiracetam batches C5152-16-243 and C5152-16-254 to invalidate the OOS results reported by your customer. After your customer returned Levetiracetam batches C5152-16-243 and C5152-16-254 you reprocessed the batches and assigned the reprocessed batches new batch numbers C5152-16-243R and C5152-16-254R. Finished API batches C5152-16-243R and C5152-16-254R were then sold to other customers.

b) you do not have scientifically sound sampling plans.

i) Sampling Procedure for API Raw Material QC-026-9 effective September 30, 2017 includes sampling instructions designed to obscure non-homogenous raw material batches. As an example, section 5.6 specifies to sample the top, middle and bottom of each compartment in the tanker and composite the compartment sample and then composite the composite samples from all the compartments. You do not have data establishing inter-batch and intra-batch homogeneity for key starting materials.

ii) Sampling procedures lack sufficient details describing how to collect samples to ensure the sampling procedure is consistently and reproducibly followed. Sampling Procedure for APIs QA-005-5 effective August 30, 2017 is silent regarding which drums to sample or how to collect samples from the sampled drums.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

c) you do not have data to support reduced testing for genotoxic and other impurities. During process validation for Valsartan you committed to testing the final API validation batches for elemental impurities and residual solvents, DMF and MTBE. After the three Valsartan validation batches you test three batches each year for elemental impurities and residual solvents. During process validation for Tadalafil you tested the finished API validation batches for potential genotoxic impurity methyl chloroacetate. After the validation batches you test three batches each year for potential genotoxic impurity methyl chloroacetate.

Supporting Evidence and Relevance:

Note: Observation 9a should read finished API batches C5152-17-214 and C5152-17-215 were then sold to other customers.

9a) Complaint No. CC-16008 received September 13, 2016 for Levetiracetam batches C5152-16-243 (0.25 ppm Ethyl Carbamate impurity) and C5152-16-254 (0.68 ppm Ethyl Carbamate impurity) failing to meet Ethyl Carbamate impurity specification ≤ 0.24 ppm identifies the complaint as a quality complaint for product quality attribute [Exhibit 128]. Dr. Li stated a Single Quadrupole LC-MS is not as sensitive as a Triple Quadrupole LC-MS and sometimes it gives false positive results.

The customer tested Levetiracetam batches C5152-16-243 and C5152-16-254 using a Triple Quadrupole LC-MS not a Single Quadrupole LC-MS. The customer provided the analytical LC-MS test method used by the customer and the chromatograms from the test results the customer's tests [Exhibit 128 page 8]. I asked Dr. Li if the firm uses an in-house test method to test Levetiracetam for Ethyl Carbamate or a USP method. Dr. Li stated the firm uses an in-house test method as the USP does not have a test for Ethyl Carbamate.

Dexcel Pharma Technologies Ltd. returned 20 drums of each Levetiracetam batch. The returned batches of Levetiracetam were assigned Return No. RC-17003 [Exhibit 180]. The lids seals (primary packaging) on all 40 drums were removed by Dexcel Pharma Technologies Ltd. The firm tested a composite sample for identity [Exhibit 180 page 2 Approval of Sampling Protocol]. The firm also tested a composite sample for water content and Related Substances. I asked Ms. GE if the firm conducted additional tests for impurities on the returned batches prior to reprocessing, and approving and releasing the batches after reprocessing. Ms. GE stated no. Ms. GE stated the batches were recrystallized. Ms. GE stated Reaction J23-201 is the reactor used for crystallization in Workshop 18. Cleaning Procedure of Levetiracetam Reactor J23-201 specifies to clean with potable water and purified water until all visible residue removed and then to air dry [Exhibit 181]. Reprocessing was completed July 11, 2017. The Cleaning Record of Levetiracetam Reaction J23-201 shows the reactor was cleaned with potable water, purified water and allowed to air dry after batches C2448-17-212R and C2448-17-213R (the intermediate Levetiracetam crude batch numbers assigned from the recrystallization step) [Exhibit 182].

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

The firm sent samples of C5152-16-243 and C5152-16-254 to an outside instrument application laboratory to conduct retesting using a Triple Quadrupole LC-MS [Exhibit 128 page 9 section 2.3]. The outside laboratory did not follow the customer's test method to conduct retesting. The outside laboratory used a Triple Quadrupole LC-MS but used a different column and a different mobile phase [Exhibit 128 page 10].

I asked Ms. GE if the firm has a quality agreement with the outside application laboratory the firm used to conduct retesting requiring all equipment used for testing is qualified, any software used with the instrument is validated, and the test method used is validated prior to reporting results. Ms. GE stated no. The firm used retest results from an outside application laboratory for Levetiracetam batches C5152-16-243 and C5152-16-254 to invalidate the OOS results reported by the firm's customer [Exhibit 128 page 11 Conclusion]. Dr. Li stated the customer insisted on returning Levetiracetam batches C5152-16-243 and C5152-16-254. Dr. Li stated the firm reprocessed the batches. Ms. GE stated the firm assigned the reprocessed batches new batch numbers C5152-16-243R and C5152-16-254R and finished API batch numbers C5152-17-214 and C5152-17-215.

9bi) Sampling Procedure for API Raw Material QC-026-9 effective September 30, 2017 states for critical materials to take a sample every five containers and composite the samples before performing identity tests [Exhibit 129 page 4 section 5.9]. Exhibit 129 pages 2-3 section 5.6 specifies to sample the top, middle and bottom of each compartment in the tanker and composite the compartment samples and then composite the composite samples from all the compartments. I asked Ms. GE if the firm has data establishing inter-batch and intra-batch homogeneity for key starting materials. Ms. GE stated no.

9bii) Sampling Procedure for APIs QA-005-5 effective August 30, 2017 is silent regarding which drums to sample or how to collect samples from the sampled drums [Exhibit 130]. Exhibit 130 page 1 section 5.2.2.1 states to sample $\sqrt{n} + 1$ samples and composite the sample prior to testing.

9c) The Validation Protocol for Valsartan Process II Zinc Chloride Process included additional testing for three validation batches in step 4 crude Valsartan for TLC (Thin Layer Chromatography) to determine the completeness of the reaction in the Tetrazole reaction and Saponification of the organic phase [Exhibit 104]. The firm conducted tests for elemental impurities and residual solvent tests for DMF (Dimethyl Formamide) and MTBE (Methyl Tert-butyl Ether) as part of process validation and then committed to testing three batches a year after process validation [Exhibit 106].

Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) specifies the firm will use full scan GC-MS mode to test the three validation batches to make sure no new genotoxic impurity is generated by the optimized process [Exhibit 112 page 12 Section 2]. I asked Mr. Dong if the firm plans to continue this test after the three process validation batches. Mr. Dong stated no.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

Tadalafil, USP specification indicates the firm will test the first three batches each year for genotoxic impurity Methyl Chloroacetate [**Exhibit 131**]. I asked Mr. Dong if the firm tested the Tadalafil validation batches for Methyl Chloroacetate. Mr. Dong stated yes. I asked Mr. Dong if the firm plans to test each batch of Tadalafil for Methyl Chloroacetate prior to approving and releasing the batch. Mr. Dong stated no.

Discussion with Management:

Mr. Du disagreed with the observation stating Dr. Li used the outside laboratory to support the firm's results.

OBSERVATION 10

Your on-going testing program to monitor the stability characteristics of APIs to confirm appropriate storage conditions and retest dates is not adequate. Specifically,

a) you subjected Valsartan API samples to conditions expected to cause degradation (forced degradation). You did not conduct full product release testing on those forced degradation samples, using validated test methods, to identify the specific product release test(s) that are stability indicating. Instead you included forced degradation samples in three HPLC test method validations for Related Substance, Assay and D-Valsartan impurity. Not all potential product degradants can be identified by HPLC test methods. Product release tests for Valsartan include tests for identification of Residual Solvents by GC-FID. You did not test forced degradation samples for Residual Solvents by GC-FID.

b) you do not always appropriately add stability study samples to your stability study program. Deviation investigation DCB02-17002 was initiated for Valsartan intermediate condensate HCl batches C20213-17-339 single unknown impurity 0.56% (specification $\leq 0.5\%$) and C20213-17-340 single unknown impurity 0.56%. You reprocessed the batches. You assigned the following batch numbers to the finished APIs made from the aforementioned Valsartan intermediate condensate HCl batches: C5355-18-024 and C5355-18-023. You did not add batches C5355-18-024 and C5355-18-023 to your stability study program.

Supporting Evidence and Relevance:

10a) Valsartan USP Method and In-house Method Quality Comparison Research Report VLDqr-10-099 (R) for both Assay and Related Substance test methods included Valsartan API samples subjected to conditions expected to cause degradation (forced degradation) [**Exhibit 118**]. I asked Mr. Q. Li if the firm conducted full product release testing on forced degradation samples for Valsartan, using validated test methods, to identify the specific product release test(s) that are stability indicating. Mr. Q. Li stated no. Dr. Li stated the firm included forced degradation samples

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

in three HPLC test method validations for Related Substance, Assay and D-Valsartan impurity. Dr. Li stated he wrote a book on including forced degradation samples as part of test method validation. Dr. Li stated including forced degradation samples as part of test method validation if the correct way to identify stability indicating test methods.

Not all potential product degradants can be identified by the firm's HPLC test methods. I asked Mr. Q. Li if the firm could identify all potential product degradants using the firm's HPLC test methods. Mr. Q. Li stated no. Product release tests for Valsartan include tests for identification of Residual Solvents by GC-FID. The firm did not test forced degradation samples using the firm's Residual Solvents by GC-FID test method.

10b) Deviation investigation DCB02-17002 was initiated for Valsartan intermediate condensate HCl batches C20213-17-339 single unknown impurity 0.56% (specification $\leq 0.5\%$) and C20213-17-340 single unknown impurity 0.56% [**Exhibit 122**]. The firm reprocessed the batches. The firm assigned the following batch numbers to the finished APIs: C5355-18-024 and C5355-18-023. I asked Ms. GE if the firm added Valsartan batches C5355-18-024 and C5355-18-023 to the firm's stability study program. Ms. GE stated no.

(JDH) **Exhibit 21 page 11** shows the summary of testing results for several batches including Valsartan batches C20213-17-339 and C20213-17-339, **page 8 item #2** states efforts to identify the impurity using LC-MS were unsuccessful, and **page 22** shows the connection between the intermediate batches and the finished batches C5355-18-024 and C5355-18-023. **Exhibits 22 -23** includes pages from the batch record for each batch for release of finished API batches C5355-18-024 and C5355-18-023. **Exhibit 24** includes a listing of current USDMF specifications for Valsartan API batches in the firm's stability study program. Valsartan batches C5355-18-024 and C5355-18-023 are not included in the firm's long-term stability program. **Exhibit 21 page 8 item #3** states the CAPA for this issue has been closed.

The firm's stability procedure **Exhibit 25 section 5.1.4** states, "For the rework products, if the evaluation shows handling methods have impact on the stability of the products, stability studies shall be carried out." However, in DCB02-17002 **Exhibit 21 page 11** the only statement regarding evaluation of the impact on stability (# 11 in the table) states "the Valsartan products in workshops 12 and 13 have been conducted for stability study (CSP-16-039) result shows product stable, therefore, this time we do not need to conduct stability study again." The impacted batches - C5355-18-024 and C5355-18-023 - were manufactured in workshop 2, as indicated by their product codes (C5355).

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

Discussion with Management:

The firm disagreed with the observation. Ms. GE shook her head no and spoke in a loud voice. Mr. Du asked the translator not to translate the firm's disagreement.

PRODUCTION SYSTEM**OBSERVATION 11**

Production deviations are not always reported and evaluated and critical deviations are not always investigated and the conclusions recorded. Specifically,

a) your production operators do not always follow batch production instructions for critical processing parameters. At approximately 16:48 on July 24, 2018, the temperature monitor for Reactor II-201 used in the manufacture of Valsartan crude HCl condensate batch C20213-18-291 displayed 64.5 degrees C. The manufacturing batch record for Valsartan crude HCl condensate showed the manufacturing process for intermediate Valsartan from chemical synthesis second step was at step 5.6 in the manufacturing process. The batch record identifies the parameters for this step as 65°C-70°C maintained for 5 ± 1 hour. The batch record also identifies this 5 ± 1 hour time duration as critical. The previous batch record entry recorded at 16:40 lists a temperature of 69.5°C. The temperature for step 5.6 is controlled by a manual steam valve.

b) on July 25, 2018 in workshop 13, a production employee was observed recording a value of 2200 liters for the amount of salt water added at step 7.7 in the batch manufacturing record during the production of crude Valsartan batch C20329-18-261. The flowmeter for the salt water displayed a value of 1.89. A production operator in Workshop 13 stated 1.89 equates to 1,890 liters. The specification for salt water at step 7.7 in the batch manufacturing record for crude Valsartan is 2200 +/- 200L.

Supporting Evidence and Relevance: (JDH)

11a) **Exhibit 26** includes batch record pages from 07/24/2018 showing the specifications of the critical process parameter and documentation of the temperature. At the time of the observation, production personnel explained the 5 hour time parameter is cumulative and that a temperature drop outside of the specified range would not prompt a restart of the 5 hour parameter. Production personnel further stated the temperature at this step is manually controlled by a steam valve which was adjusted shortly before the I observed the temperature excursion.

11b) **Exhibit 27 photograph** includes the page of the batch record from 07/25/2018 showing the recorded value of 2200 liters of salt water at step 7.7. The flowmeter reading was cleared shortly after I observed the reading and before I was unable to photograph the flowmeter reading.

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

Discussion with Management:

Ms. GE disagreed with the observation stating the operator charged the salt water in two parts. I asked Ms. GE if the operator documented the first addition salt water addition and then the second addition on the batch record. Ms. GE stated no. I asked Ms. GE if the operator should have documented the two separate salt water additions on the batch record. Ms. GE stated yes.

REFUSALS

There were no refusals.

GENERAL DISCUSSION WITH MANAGEMENT

On August 3, 2018, a close out discussion was held with management. A Form FDA 483, Inspectional Observations, was issued to Mr. Jun Du, Executive Vice President. Each point was previously discussed during the inspection. Mr. Du stated the firm is continuously improving cGMPs. Mr. Du stated he did not agree with some points in the Form FDA 483, Inspectional Observations. Mr. Du stated he will look at the details and determine a way to maintain a GMP system and provide a quality product. Mr. Du stated the firm has learned a lot through the NDMA issue and the firm will look to set-up a separate system to look at genotoxic impurities in the future. Mr. Du stated the firm will provide a written response. I explained the items listed on the Form FDA 483 were our observations of objectionable conditions and would be further reviewed by the FDA. I also notified the firm after further review, these observations could be considered violations of the Food, Drug & Cosmetic Act or other statutes. I warned if these observations are considered violations, FDA may take action without further notice which may include re-inspection, warning letter, and/or detention/refusal of product upon entry to the United States. Mr. Du stated he understood. **Exhibit 167** is a list of those present for the close out discussion.

ADDITIONAL INFORMATION

The officially sealed original copies and unsealed working copies of discs containing photographs taken during the inspection and documents collected at the firm are filed with the unlabeled exhibits and attachments.

LOGISTICS

Accommodations were at Zhejiang Taizhou Marriott hotel located at 55 Tianyuan Road, Hyuangyan D Taizhou 318020 China. The hotel is approximately a 4.5 hour drive from the Shanghai airport,

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

and about a one hour drive from the firm. The firm provided transportation to and from the airport and the firm each day. The hotel has several restaurants.

SAMPLES COLLECTED

(JDH) The following samples were collected during the inspection:

1076070: Sample consists of two sub-subsamples of Valsartan API batch C5069-15-053M, manufacture date 06/05/2016, collected from the firms retain sample. Sub-sample A consists of approximately 2.49 grams and sub-sample B contains approximately 1.13 grams. This batch was manufactured in 2015 using the triethylamine process.

1076071: Sample consists of two sub-subsamples of Valsartan API batch D5191-18-110, manufacture date 05/04/2018, collected from the firms retain sample. Sub-sample A consists of approximately 1.14 grams and sub-sample B contains approximately 1.23 grams. This batch was manufactured in workshop W02 and the firm's testing found this batch to contain 20.1 ppm NDMA [Exhibit 43].

1076072: Sample consists of two sub-subsamples of Valsartan API batch C5523-17-522, manufacture date 08/12/2017, collected from the firms retain sample. Sub-sample A consists of approximately 1.75 grams and sub-sample B contains approximately 1.92 grams. This batch was manufactured in workshop 13 and the firm's testing found this batch to contain 104.3 ppm NDMA [Exhibit 44].

1076073: Sample consists of two sub-subsamples of Valsartan API batch C5355-17-306, manufacture date 10/26/2018, collected from the firms retain sample. Sub-sample A consists of approximately 2.26 grams and sub-sample B consists of approximately 1.82 grams. This batch was manufactured in workshop 2 and the firm's testing found this batch to contain 118.2 ppm NDMA [Exhibit 45].

The samples listed were collected from the firm's retain samples. I observed firm personnel collect the samples. Valsartan retain samples consisted of approximately 60 grams of Valsartan per batch. Each sample was packaged in a heat-sealed polyethylene bag, and enclosed in an heat-sealed aluminum foil bag. A photo of the intact retain sample package for batch C5069-15-053M (sample 1076070) is shown here as an example:

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

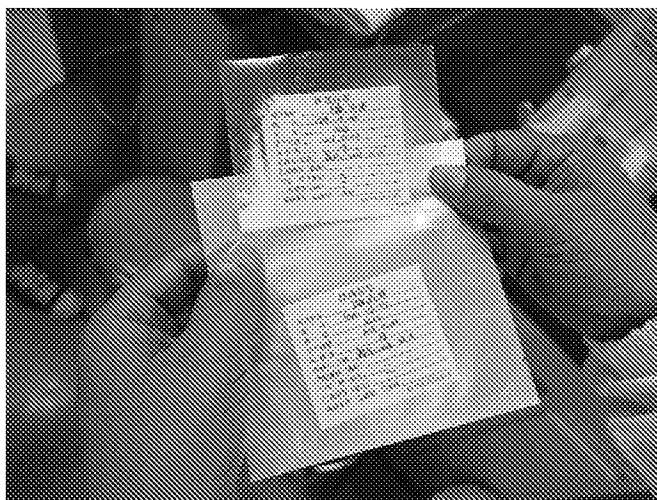
FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018



After opening the retain package and weighing the samples on a calibrated and verified balance, the samples were packaged in a similar manner; a heat-sealed polyethylene bag inside a heat-sealed aluminum foil bag as shown here:



The following samples consisted of intact bottles of reference standards available at the firm:

1076074: Consists of 4/500 mg bottles of Valsartan API reference standard, batch 2018-5045

1076075: Consists of 4/50 mg bottles of D-Valsartan impurity reference standard, batch 2017-5083

1076076: Consists of 4/50 mg bottles of Benzyl-Valsartan impurity reference standard, batch 2017-5226

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

1076077: Consists of 4/50 mg bottles of Butyryl-Valsartan impurity reference standard, batch 2017-5102

The samples were submitted to the FDA Division of Pharmaceutical Analysis in St. Louis, MO.

VOLUNTARY CORRECTIONS

Voluntary corrections to the previous inspection were not adequate. Facilities and equipment are not always properly maintained. The firm continues to invalidate OOS (Out-of-Specification) investigations without scientifically sound justifications. Due to time constraints I did not review the firm's controls over laboratory instruments to prevent data integrity issues.

EXHIBITS COLLECTED

EXHIBIT 1 Cleaning procedure for Valsartan reactor W02-203-1,2,3, 14 pages
EXHIBIT 2 Cleaning procedure for Valsartan reactor W02-204-1,2,3, 14 pages
EXHIBIT 3 Photograph Valsartan Cleaning SOP, 1 page
EXHIBIT 4 Photos cleaning validation report for reactors, 4 pages
EXHIBIT 5 Photo equipment use log reactor W02-203-1 - 1, 1 page
EXHIBIT 6 Photos equipment use log for reactor W02-203-1 - 2, 2 pages
EXHIBIT 7 Photos equipment use log for reactor W02-204-3 - 2, 2 pages
EXHIBIT 8 Cleaning SOP reactor W02-201-1 and W02-201-2 - 7, 7 pages
EXHIBIT 9 Cleaning SOP reactor II-250, 6 pages
EXHIBIT 10 Photo status tag for reactor W02-102-1 - 1, 1 page
EXHIBIT 11 Photo particulates reactor W02-102-1 - 1, 1 page
EXHIBIT 12 Photo clean status of reactor W02-102-2, 1 page
EXHIBIT 13 Photo white residue reactor W02- 102-1, 1 page
EXHIBIT 14 Photo equipment use logs for reactors W02-102-1 and W02-102-2, 2 pages
EXHIBIT 15 Photo clean status of reactor II-250, 1 page
EXHIBIT 16 Photo inside reactor II-250, 1 page
EXHIBIT 17 Photo equipment use log reactor II-250, 1 page
EXHIBIT 18 Photos repaired agitator shaft reactor II 250, 2 pages
EXHIBIT 19 Photo reactor II-250 maintenance log, 1 page
EXHIBIT 20 Info page glass-liner repair, 1 page
EXHIBIT 21 Deviation investigation DCB02-17002, 24 pages
EXHIBIT 22 Batch release batch C5355-18-024, 3 pages
EXHIBIT 23 Batch release batch C5355-18-023 - 3, 3 pages
EXHIBIT 24 USDMF Valsartan batches on stability, 1 page
EXHIBIT 25 Stability SOP, 18 pages

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745
EI Start: 07/23/2018

EI End: 08/03/2018

EXHIBIT 26 Temperature drop Valsartan step 2 - 2, 2 pages
EXHIBIT 27 Photo inaccurate recording of salt water wash 7.25.18, 1 page
EXHIBIT 28 Example process flow chart for DMF-Zinc Cl process, 7 pages
EXHIBIT 29 Comparison chart of processes, 1 page
EXHIBIT 30 Deviation DCZ-18001, 120 pages
EXHIBIT 31 Example process flow chart for separated quenching process, 7 pages
EXHIBIT 32 Workshop 2 MBR for crude Valsartan, 34 pages
EXHIBIT 33 Workshop 13 MBR for crude Valsartan, 34 pages
EXHIBIT 34 Workshop W02 MBR for crude Valsartan, 36 pages
EXHIBIT 35 Translated workshop 2 MBR showing DMF steps, 10 pages
EXHIBIT 36 Translated workshop 13 MBR showing DMF steps, 10 pages
EXHIBIT 37 Translated workshop W02 MBR showing DMF steps, 8 pages
EXHIBIT 38 Change control for workshop 12 renovation, 18 pages
EXHIBIT 39 Optimized MBR for crude Valsartan, workshop 2, 33 pages
EXHIBIT 40 Example translated MBR for optimized crude Valsartan, workshop 2, 33 pages
EXHIBIT 41 DMF change history, 4 pages
EXHIBIT 42 List of customers for USP spec Valsartan, 3 pages
EXHIBIT 43 NDMA testing record for batch D5191-18-110, 1 page
EXHIBIT 44 NDMA testing record for batch C5523-17-522, 1 page
EXHIBIT 45 NDMA testing record for batch C5355-17-306, 1 page
EXHIBIT 46 CD containing spreadsheet with NDMA test results, 1 page
EXHIBIT 47 CD containing photos taken during the inspection, 1 page
EXHIBIT NUMBERS 48-100 NOT USED
EXHIBIT 101 PCRC-11025, 54 pages
EXHIBIT 102 Lab Contract, 9 pages
EXHIBIT 103 Acceptance Criteria CNVP-11-074, 3 pages
EXHIBIT 104 Validation Protocol CNVP-11-075, 146 pages
EXHIBIT 105 Research Report, 23 pages
EXHIBIT 106 Valsartan Quality Standard, 2 pages
EXHIBIT 107 Change Control SOP, 21 pages
EXHIBIT 108 DMF Amendment, 26 pages
EXHIBIT 109 Risk Management SOP, 54 pages
EXHIBIT 110 Valsartan Product Development Report, 46 pages
EXHIBIT 111 Deviation DCB18-17017, 30 pages
EXHIBIT 112 Validation Protocol PVC-18012(P), 14 pages
EXHIBIT 113 Deviation DCE-18001, 120 pages
EXHIBIT 114 TEA Comparison, 7 pages
EXHIBIT 115 DMF Reprocessing, 1 page
EXHIBIT 116 Change PCRC-18021, 47 pages
EXHIBIT 117 Tadalafil OOT, 1 page
EXHIBIT 118 Test Method Validation, 21 pages

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

EXHIBIT 119 Deviation DCB18-17025, 34 pages
EXHIBIT 120 Deviation DDW02-17003, 20 pages
EXHIBIT 121 Deviation SOP, 21 pages
EXHIBIT 122 Deviation DCB02-17002, 24 pages
EXHIBIT 123 Returns SOP, 14 pages
EXHIBIT 124 Return RC-18006, 10 pages
EXHIBIT 125 Valsartan C5069-15-037MM, 50 pages
EXHIBIT 126 Valsartan C5069-15-037MMM, 29 pages
EXHIBIT 127 CoA Ethylene Glycol, 9 pages
EXHIBIT 128 Complaint CC-16008, 17 pages
EXHIBIT 129 Raw Material Sampling SOP, 24 pages
EXHIBIT 130 Sampling APIs SOP, 9 pages
EXHIBIT 131 Tadalafil Specification, 1 page
EXHIBIT 132 Opening Meeting Attendees, 2 pages
EXHIBIT 133 Mr. Du Job Description, 3 pages
EXHIBIT 134 Ms. GE Job Description, 4 pages
EXHIBIT 135 Board of Directors, 1 page
EXHIBIT 136 Organizational Chart, 1 page
EXHIBIT 137 Consignees, 1 page
EXHIBIT 138 Product List, 3 pages
EXHIBIT 139 Valsartan Sales 2016-2018, 298 pages
EXHIBIT 140 Valsartan Shipment, 8 pages
EXHIBIT 141 Valsartan Labels, 2 pages
EXHIBIT 142 Tadalafil Shared Equipment List, 2 pages
EXHIBIT 143 Valsartan Dedicated Equipment List in Each Workshop, 9 pages
EXHIBIT 144 Novartis Invoices, 70 pages
EXHIBIT 145 Novartis Purchase Orders, 48 pages
EXHIBIT 146 Valsartan Inventory, 9 pages
EXHIBIT 147 Valsartan Inventory East Zone, 30 pages
EXHIBIT NUMBER 148 NOT USED
EXHIBIT 149 CDER Communications, 24 pages
EXHIBIT NUMBERS 150 – 158 NOT USED
EXHIBIT 159 Communication Timeline, 54 pages
EXHIBIT 160 Valsartan OOS List 2016-2018, 5 pages
EXHIBIT 161 Comparison Valsartan Specifications, 2 pages
EXHIBIT 162 Recall Press Release, 5 pages
EXHIBIT 163 Chinese FDA Approval, 3 pages
EXHIBIT 164 GC Method, 3 pages
EXHIBIT 165 GC-FID Chromatograms, 19 pages
EXHIBIT 166 Novartis Test Results, 17 pages
EXHIBIT 167 Close-out Meeting Attendees, 3 pages

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

EXHIBIT 168 BR Version Numbers, 6 pages
EXHIBIT 169 Solvents for DMF Version, 1 page
EXHIBIT 170 Solvents Used Each Workshop, 1 page
EXHIBIT 171 Reprocessing SOP, 19 pages
EXHIBIT 172 Validation Triple Quadrupole Ethyl Carbamate Method, 61 pages
EXHIBIT 173 APQR SOP, 26 pages
EXHIBIT 174 Complaint SOP, 12 pages
EXHIBIT 175 Recall SOP, 22 pages
EXHIBIT 176 Valsartan Impurity Profile, 38 pages
EXHIBIT 177 CoA Before & After Process Change, 6 pages
EXHIBIT 178 Return RD-17005, 24 pages
EXHIBIT 179 Repackaging BR, 14 pages
EXHIBIT 180 Return RC-17003, 14 pages
EXHIBIT 181 Cleaning SOP J23-201, 5 pages
EXHIBIT 182 Cleaning Record J23-201, 2 pages
EXHIBIT 183 Photos taken at Zhejiang Pharmaceutical Co., Ltd., 3 pages
EXHIBIT 184 Chromatograph SOP, 17 pages
EXHIBIT 185 HPLC Injection History, 1878 pages
EXHIBIT 186 Rejected or Returned API, 2 pages
EXHIBIT 187 Torrent Shipments, 13 pages
EXHIBIT 188 Reserve Sample SOP, 12 pages

ATTACHMENTS

ATTACHMENT 1 Form FDA 483, Inspectional Observations, 11 pages
ATTACHMENT 2 For-Cause Inspection Memo, 7 pages
ATTACHMENT 3 Form FDA 484, Recpt. Samples, 1 page
ATTACHMENT 4 AMENDED Form FDA 483, Inspectional Observations, 11 pages
ATTACHMENT 5 Cover Letter for Amendment to Form FDA 483, 1 page

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co.,
Ltd., Coastal Industrial Zone, Chuannan
No. 1 Branch No. 9, Donghai 5th Avenue,
Linhai, Taizhou, Zhejiang 317016 China

FEI: 3003885745

EI Start: 07/23/2018

EI End: 08/03/2018

**Cheryl A.
Clausen
-S**

Digitally signed by Cheryl A.
Clausen -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2
001563195, cn=Cheryl A.
Clausen -S
Date: 2018.08.20 05:53:02
-04'00'

Cheryl A. Clausen
Investigator

**Joel D.
Hustedt
-S**

Digitally signed by Joel D.
Hustedt -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=
1300419447, cn=Joel D.
Hustedt -S
Date: 2018.08.21 07:41:02
+08'00'

Joel D. Hustedt
Investigator

Exhibit 4

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE**

**IN RE: VALSARTAN, LOSARTAN,
AND IRBESARTAN PRODUCTS
LIABILITY LITIGATION**

MDL No. 2875

Honorable Robert B. Kugler,
District Court Judge

This Document Relates to All Actions

STIPULATION OF ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD.

Pursuant to Special Master Report and Order No. 56, in exchange for Plaintiffs' agreement not to further examine a witness at deposition regarding the statements identified herein, Defendant Zhejiang Huahai Pharmaceutical Co., Ltd. ("ZHP") hereby stipulates as follows:

1. ZHP states that there are no health benefits associated with the presence of NDMA or NDEA in valsartan.
2. ZHP states that the publication *Purification of Laboratory Chemicals* (4th ed.) by W.L.F. Armarego and D.D. Perrin, which was first published in 1996 and documented scientific knowledge at that time, states on page 192 that DMF

“[d]ecomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide.”

3. ZHP states that it was required to perform a risk assessment in connection with the process change to the zinc chloride process. ZHP further states the following:
 - a. ZHP states that the scientific research relied on to use DMF as part of the zinc chloride process did not include scientific research into the potential decomposition products of DMF under the conditions of the zinc chloride process.
 - b. The risk assessment of DMF did not specifically evaluate whether DMF was degrading to yield dimethylamine as part of the zinc chloride process.
 - c. Therefore, there is no document from Shanghai SynCores or ZHP that documents that potential degradation of DMF as part of the zinc chloride process was evaluated as part of the risk assessment for the zinc chloride process.
 - d. ZHP states that it did not perform a risk assessment on the potential degradation of DMF because it did not realize that DMF would degrade in the way it ultimately degraded in the zinc chloride manufacturing process of valsartan. ZHP is not saying that it was not possible to know that DMF could degrade.
 - e. ZHP never identified the nitrosamine impurities in connection with its 2011 Risk Assessment and therefore did not evaluate the nitrosamine impurities as part of any steps of the risk assessment process.

4. With regard to the Change Request Form identified as Exhibit 195 to the March 28/29, 2021 deposition of Peng Dong (copy of Exhibit attached hereto as Exhibit 1), ZHP states the following:

- a. The “Explanation Section” in Section 2 of the Change Request form on the page bearing Bates number ZHP01843067 provides a summary of the explanation for why the process change from the triethylamine hydrochloride process to the zinc chloride process was undertaken.
- b. One of the reasons for the quality review described in Section 3 of the Change Request Form on the page bearing Bates number ZHP01843069 was to identify impurities due to the new process.
- c. Section 3 of the Change Request Form on the page bearing Bates number ZHP01843070 provided that if this change was against cGMP code, it was supposed to be rejected.

Dated: May 13, 2022	<u>/s/ Richard T. Bernardo</u> Richard T. Bernardo SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP One Manhattan West New York, NY 10001-8602 richard.bernardo@skadden.com Jessica D. Miller SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP 1440 New York Avenue, N.W. Washington, D.C. 20005 jessica.miller@skadden.com Counsel for Defendant
---------------------	--

Exhibit 6

Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities Resulting from the Sodium Azide Quenching in Crude Irbesartan

Jinsheng LIN

To: Jucai GE, Tianpei HUANG, Wangwei CHEN, Wenquan ZHU, Wenbin CHEN, Mr. Li, Peng DONG, Lihong LIN, Yanfeng LIU, Peng WANG, Wenling ZHANG 07/27/2017 Detailed Information

Valsartan Impurity K.pdf (846 KB)

Ms. Ge:

According to the results of our telephone communication with the Technology Department of Chuannan Plant 1 today, due to the incomplete quenching of sodium azide caused by the separate treatment of irbesartan sodium azide wastewater, there is the frequent occurrence of muffled explosion in the production process, so the Technology Department carried out the technical improvement by which the sodium azide quenching takes place in the unstratified step in the crude irbesartan process. However, after the improvement, there is an unknown impurity of about 0.544% at 26 minutes in the crude irbesartan, and it is the largest impurity in the irbesartan crude product.

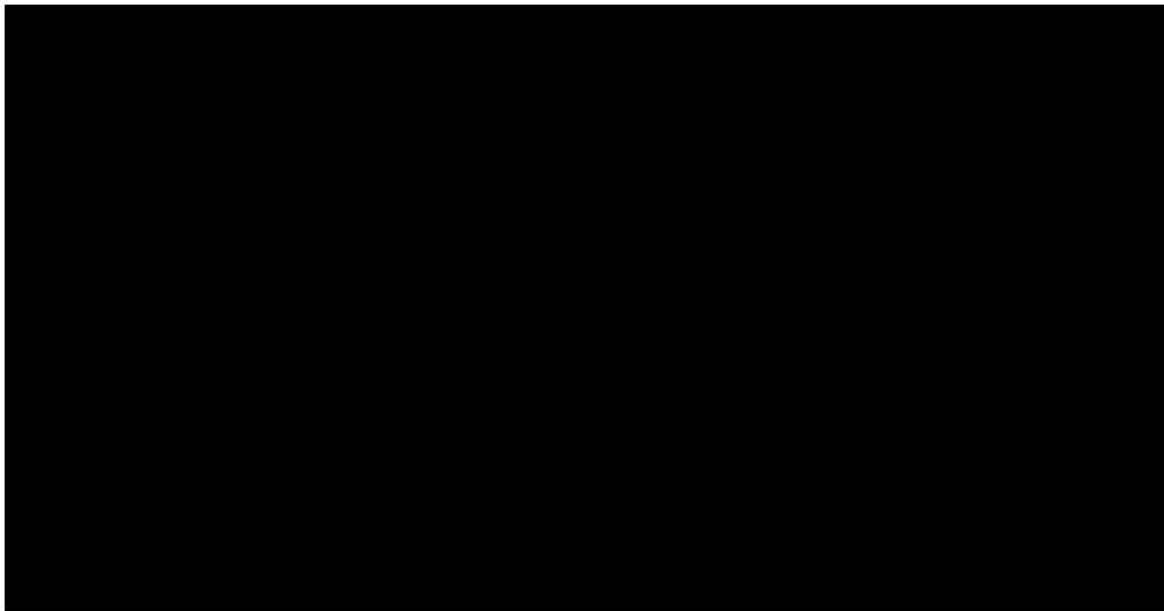
[REDACTED]

[REDACTED]

[REDACTED]

Min Li
ZHP-296
4/20/2021

Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic. Its possible formation route is shown as follows:



In order to further verify the structure of the impurity and its formation mechanism, we plan to simulate the quenching conditions and use the finished Irbesartan product to react with NaNO_2 and HCl to monitor the impurity produced by the reaction, and then separate it for NMR for final structural verification, while simultaneously carrying out the confirmation of the impurity by multi-stage MS.

If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an extremely high GMP risk. This is a common problem in the production and synthesis of sartan APIs. It is recommended to improve other quenching processes (such as NaClO) along with the optimization of the valsartan sodium azide quenching process.

I've also attached a patent of a 2013 sodium azide NaClO quenching method by Zhejiang Second Pharma Co., Ltd. they proposed that the use of NaNO_2 quenching will result in the formation of N-NO impurities. At the same time, they used ZHP's crude Valsartan in their LC-MS test and detected this impurity. This indicates that other companies have paid attention to the quality problem very early on. So leaders please pay attention to this issue.

Jinsheng LIN

CEMAT

2017/07/27

Exhibit 7

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND
IRBESARTAN PRODUCTS LIABILITY
LITIGATION

MDL No. 2875

Honorable Robert B. Kugler,
District Court Judge

Honorable Karen M. Williams,
Magistrate Judge

Honorable Thomas Vanaskie (Ret.),
Special Discovery Master

DECLARATION OF SETH A. GOLDBERG

I, Seth A. Goldberg, of full age, hereby declare as follows:

1. I am an attorney at law of the State of New Jersey, a member of good standing of the bar of this Court, a Partner with the law firm of Duane Morris LLP, and counsel to Defendants Zhejiang Huahai Pharmaceutical Co., Ltd. (“ZHP”), Princeton Pharmaceutical Inc. (“Princeton”), Solco Healthcare U.S. (“Solco”), and Huahai U.S. Inc. (“Huahai U.S.”, and collectively with ZHP, Princeton, and Solco, “the ZHP Parties”).

2. I make this Declaration based on personal knowledge and in support of the ZHP Parties’ Cross Motion for Protective Order to Preclude the Production of the Custodial File of Baohua Chen.

3. A true and correct copy of the final transcript of Jucai Ge’s deposition testimony on April 30, 2021 is attached to this Declaration as **Exhibit A**.

4. A true and correct copy of the final transcript of Lihong (Linda) Lin’s deposition testimony on May 4, 2021 is attached to this Declaration as **Exhibit B**.

5. A true and correct copy of the final transcript of Min Li's deposition testimony on April 22, 2021 is attached to this Declaration as **Exhibit C**.

6. A true and correct copy of the final transcript of Eric Gu's deposition testimony on April 5, 2021 is attached to this Declaration as **Exhibit D**.

7. A true and correct copy of the final transcript of Hai Wang's deposition testimony on March 11, 2021 is attached to this Declaration as **Exhibit E**.

8. A true and correct copy of the final transcript of John Iozzia's deposition testimony on January 20, 2021 is attached to this Declaration as **Exhibit F**.

9. Attached to this Declaration as **Exhibit G** is a table listing the titles held by Baohua Chen in various public bodies.

10. Attached to this Declaration as **Exhibit H** is an index cataloging the volumes of the ZHP Parties' productions to date in this litigation.

11. Attached to this Declaration as **Exhibit I** is a list of the custodial files collected in connection with the ZHP Parties' productions in this litigation.

12. Attached to this Declaration as **Exhibit J** is a table illustrating the references to Baohua Chen in the exhibits introduced at the depositions of the ZHP Parties witnesses.

13. A true and correct copy of an English language translation of an e-mail dated July 27, 2017, authored by ZHP employee Jinsheng Lin (ZHP00190573) is attached to this Declaration as **Exhibit K**.

14. A true and correct copy of an e-mail dated April 23, 2021 from Plaintiffs' counsel to counsel for the ZHP Parties is attached to this Declaration as **Exhibit L**.

15. A true and correct copy of a declaration executed by Linhong (Linda) Lin, the Director of Regulatory Affairs of ZHP, is attached to this Declaration as **Exhibit M**.

16. A true and correct copy of a declaration executed by Yang Xueyu, a partner of Yu Zheng Law Firm, is attached to this Declaration as **Exhibit N**.

17. Attached to this Declaration as **Exhibit O** is a table comparing the volume of correspondence including Baohua Chen to the total production volume of the ZHP Parties to date in this litigation.

Executed on May 14, 2021.

Respectfully submitted,

/s/ Seth A. Goldberg
Seth A. Goldberg, Esq.
Lead Counsel and Liaison
Counsel for Defendants

DUANE MORRIS LLP

Seth A. Goldberg, *Lead Counsel and*
Liaison Counsel for Defendants
30 South 17th Street
Philadelphia, Pennsylvania 19103
Tel.: (215) 979-1000
Fax: (215) 979-1020
SAGoldberg@duanemorris.com

Attorneys for Zhejiang Huahai
Pharmaceutical Co, Ltd., Princeton
Pharmaceutical Inc., and Solco
Healthcare US, LLC

EXHIBIT K

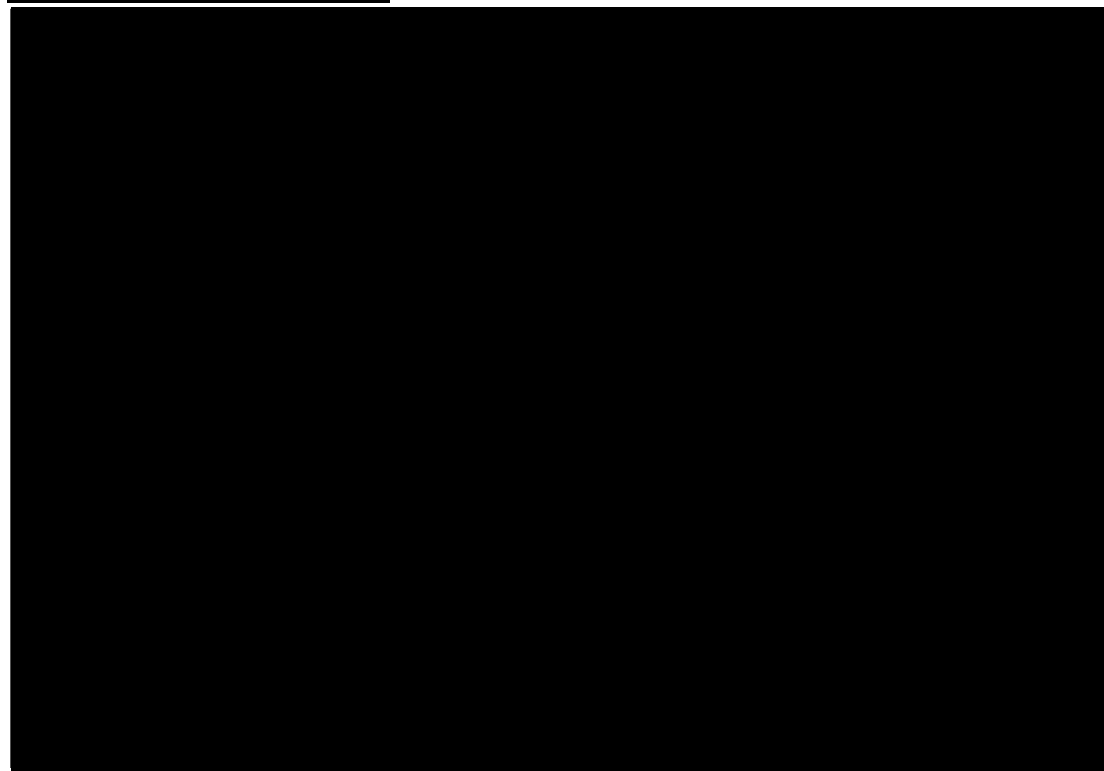
Bulletin on the preliminary findings about produced unknown impurities in quenching sodium azide for the crude irbesartan**Lin Jinsheng**

July 27, 2017, 4:17 PM Detailed information

To: Ge Jucai, Huang Tianpei, Chen Wangwei, Zhu Wenquan, Chen Wenbin, Li Zong, Dong Peng, Lin Lihong, Liu Yanfeng, Wang Peng, Zhang Wenling
[icon] Valsartan Impurities K.pdf (846 KB)

General Manager Ge:

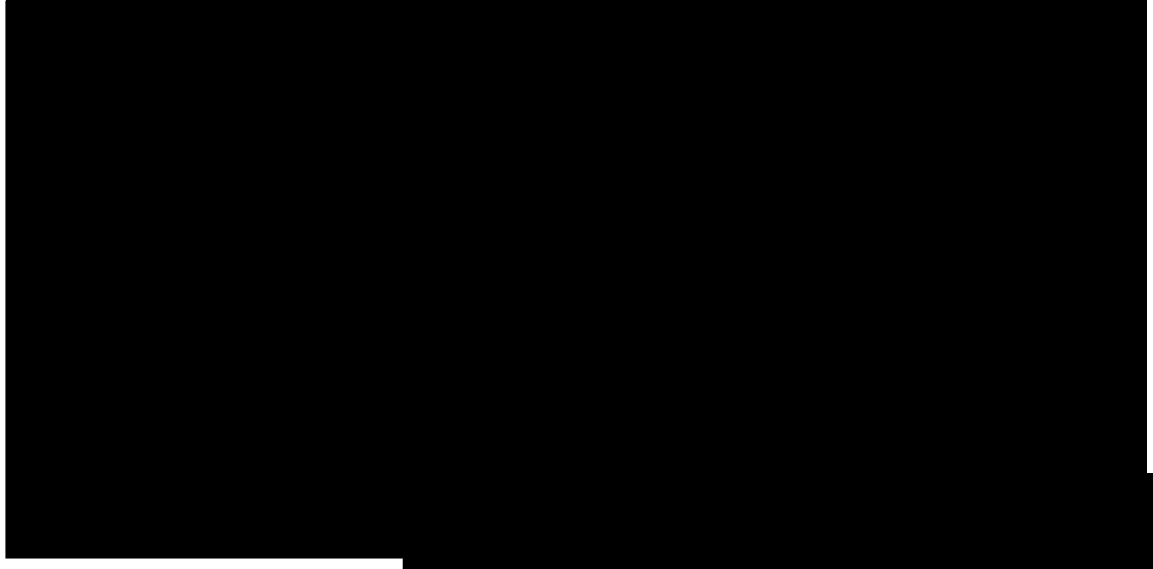
According to the results in our telephone communication with the Chuannan (Southern Sichuan)-Technical Department I today, because the separate treatment of sodium azide wastewater of irbesartan resulted in incomplete quenching of sodium azide, resulting in frequent depressed blast in the production process, thus, the technical department carried out technical transformation to quench sodium azide in the no stratification process of the crude irbesartan process, however, after the transformation, 0.544% of unknown impurities are produced in the crude irbesartan at 26 min, and it is the biggest impurity in the crude irbesartan..



RESTRICTED CONFIDENTIAL INFORMATION

ZHP00190573

Through the secondary mass spectrometry analysis, it can be inferred that the additional NO substituent is in the cyclic compound fragment part, and it is probably that it is the N-NO compound, similar to the N- nitrosodimethylamine group produced by the quenching of valsartan with sodium nitrite, its structure is very toxic, and its possible production pathways are as follows:



In order to further confirm the structure of the impurity and the principle of its generation, we plan to simulate the quenching conditions to react NaNO_2 and HCl with the finished product of irbesartan, to monitor the impurities produced by the reaction, and then separate them for NMR for final structural confirmation, simultaneously, carry out the confirmation of impurity by multi-stage mass spectrometry.

If it is confirmed as the above speculated structure, its toxicity will be very strong, and GMP risk is great. This is a common problem in the production and synthesis of sartan API. It is recommended to improve to other quenching method, such as NaClO , in addition to optimize the quenching process for sodium azide in valsartan.

Attached is a patent method for quenching sodium azide with NaClO by Xinsaike Pharmaceutical in 2013. they proposed that the use of NaNO_2 quenching will produce N-NO impurities, in the meanwhile, our Huahai crude valsartan was detected by LC-MS. The impurity was indeed found, indicating that other companies have paid attention to this quality issue a long time ago. Leaders are also requested to pay attention to it.

Lin Jinsheng
CEMAT
July 27, 2017

Exhibit 9

Min Li

ZHP-292

4/20/2021

Min Li, Ph.D.*Home Address:*

88 Becks Blvd.
Ringo, NJ 08551
(908) 284-2283

Work Address:

Huahai Pharmaceutical Co., Ltd.
Xunqiao, Linhai
Zhejiang, China 317024
(86) 188-58621863

Summary: Author of a book entitled "*Organic Chemistry of Drug Degradation*", a comprehensive and in-depth book in the field of drug stability and degradation mechanisms, which was published in 2012 by the Royal Society of Chemistry. Primary/communicating author or inventor of more than 50 papers and patents. Thirty years of multi-disciplinary research and development experience in drug design and development, drug degradation mechanism studies, pharmaceutical impurity identification, analytical method development and validation, and support for new drug regulatory filings. Between 1998 and 2014, I had led several teams of senior level scientists at Merck and Schering-Plough for various research and development projects including studies of drug degradation pathways, elucidation of drug degradant and impurity structures, troubleshooting atypical and out-of-specification (OOS) events during manufacturing processes of both drug substances and products, studies of gas phase ion chemistry/fragmentation pathways of organic molecules via LC-MSⁿ, analytical method and specification development, and support for the CMC sections of new drug filings. Since September 2014, I took the position of VP, Analytical Operation at Huahai Pharmaceutical Co., Inc., a leading Chinese pharmaceutical manufacturer with operations in both China and US, overseeing analytical R&D and providing technical leadership in API quality control operations.

Education:

1987-1991 **Ph.D.** Organic/Bioorganic Chemistry, The Johns Hopkins University, Baltimore, Maryland.

Design and synthesis of covalent inhibitors of serine proteases and identification of active site amino acid residuals through the use of HPLC, FAB-MS, ¹³C-NMR, and amino acid analysis and sequencing.

1984-1986 In **M.S.** Program in Polymer Chemistry, Institute of Material Sciences, Fudan University, Shanghai, China.

1980-1984 **B.S.** Chemistry, Fudan University, Shanghai, China.

Professional Experience:

2014-Present *Vice President, Analytical Operation.* Huahai Pharmaceutical Co., Ltd, Linhai, Zhejiang, China. Overseeing company-wide analytical R&D and providing technical leadership in API quality control operations.

2005-2014 *Associate Director.* Merck & Co., Inc., ACDS – Supply Analytical Sciences, New Jersey (2005-2009 *Manager.* Schering-Plough Corporation, Global Quality Services - Analytical Sciences, New Jersey. Schering-Plough merged with Merck in Nov. 2009. The department name was changed but its function remained the same).

Led several technical teams of scientists (majority were senior level Ph.D. scientists) supporting Merck's global manufacturing sites for various laboratory and manufacturing atypical and OOS investigations, analytical method development and validation, and manufacturing process improvement. My laboratory was very well equipped with the state-of-art analytical instruments including 9 mass spectrometers of different capabilities (e.g., Thermo LTQ/Orbitrap, Thermo Exactive, Waters MALDI-TOF, and Waters Q-Tof Premier time-of-flight mass spectrometers). Providing guidance and strategies in drug degradation studies using multi-disciplinary approaches including chromatography, LC-MS/MS, 1D- and 2D-NMR, and organic chemistry techniques (mechanism-based stress studies). Played a key leadership role in the completion of several hundreds of technically challenging projects involving identification of unknown pharmaceutical impurities (process impurities, degradants and extractables/leachables), elucidation of drug degradation mechanisms, and development and validation of analytical methods. The successful completion of these investigations prevented potential stock-out situations and provided the basis for continuous improvement of manufacturing processes. Participated in a number of cross-functional Drug Development and Commercialization (DCT) teams responsible for drug development strategy, NDA/MAA filings, technology transfers, and timeline and resource management. Acted as a subject-matter-expert in company's global API outsourcing team responsible for reviewing and approval of suppliers' CMC documents and supporting technical documents.

1998-2005 *Scientific Fellow.* Merck & Co., Inc., Regulatory & Analytical Sciences, Merck Manufacturing Division, West Point, Pennsylvania.

Managed a technical group responsible for analytical and manufacturing support of drug products in the categories of Anti-Inflammatory, Neuroscience, Oncology, and Cholesterol-Lowering. Conducted analytical research, development, and method validation in drug substances as well as in formulated products. Performed technical investigation and pharmaceutical research regarding drug stability, degradation, and drug-excipient interaction. Identification of drug degradants and impurities by using LC-MS/MS and NMR. Provided technical leadership in the review of compendial, NDA, and annual regulatory filing documents. In charge of several new product analytical methodology transfer projects to production and stability testing sites. Participated in a number of cross-functional teams that were responsible for raw material outsourcing, source of supply change, specification setting, and new drug development strategies.

1995-1998 *Principal Scientist.* Roche Diagnostics. Drug Monitoring Research & Development, Somerville, New Jersey.

Performed stability and degradation study of drugs in buffer and urine samples with diode-array HPLC. Conducted study in solid phase extraction of drug substances (from urine samples) and environmental pollutants (from soil and water samples). Carried out analysis and purification of various organic compounds and bioconjugates using analytical and preparative HPLC. Performed basic and applied research in immunochemistry and protein bioconjugate chemistry. Conducted process research for manufacture of

chemical reagents used in immunochemical diagnostic kits. Performed diagnostic reagent production with GMP compliance. Supervised and mentored junior chemists.

1994-1995 *Research Chemist.* Symphony Pharmaceuticals Inc., Pennsylvania.
Design and synthesis of AMPA receptor antagonists as novel neural protective agents.

1991-1994 *Postdoctoral Research Associate.* University of Illinois at Chicago. Department of Medicinal Chemistry, College of Pharmacy.
(1) Using photoaffinity labeling technique and subsequent HPLC and MS analysis, a binding site of 5-bromotryptophan (a potent anti-sickling agent) in hemoglobin was determined, which provided a basis for rational design of more potent anti-sickling agents. (2) With computer-aided rational design, a class of promising thrombin inhibitors were designed and synthesized.

Awards and Honors:

- Twenty Shining Performance Awards at Schering-Plough, 2005 through 2010.
- Recipient of the Sarah & Adolph Roseman Achievement Award for Excellence in Research, The Johns Hopkins University, May, 1991.
- D. Mead Johnson Fellowship, June, 1988 to August, 1991.

Technical Expertise:

- Extensive experience in structure elucidation of pharmaceutical impurities and studies of drug degradation mechanisms using various analytical techniques, such as LC-MS/MS, NMR (1D + 2D), IR, and UV-Vis.
- Design and synthesis of mimetics and derivatives of amino acids and peptides as enzyme inhibitors and protein labeling reagents.
- Experience in computer modeling for *de novo* drug design.
- Extensive experience in study of gas phase ion chemistry/fragmentation pathways of organic molecules via LC-MSⁿ.
- Extensive experience in protein bioconjugate chemistry and working knowledge of enzyme kinetics.
- Extensive experience in analytical method development and validation for drug substances and drug products in GMP environment.
- Purification and analysis of proteins and peptides using electrophoresis, gel-filtration, ion exchange, and reversed phase chromatography.
- Experience in analysis (including sequencing) of proteins and peptides with mass spectrometry (FAB, ESI, and MALDI-TOF).
- Experience in organophosphorus chemistry, heterocyclic chemistry, and organic photochemistry.
- Working knowledge of Process Analytical Technology (PAT) and Quality by Design (QbD).

Professional Affiliation:

- Member of United States Pharmacopeia Chemical Medicines Monographs Expert Committee for the 2015 – 2020 and 2020 – 2025 Cycles.

Exhibit 11



U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via UPS
Return Receipt Requested

Warning Letter: 320-19-04

November 29, 2018

Mr. Jun Du
Executive Vice President
Zhejiang Huahai Pharmaceutical Co., Ltd.
Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai Fifth Avenue, Linhai, Taizhou Zhejiang 317016
CHINA

Dear Mr. Du:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, from July 23 to August 3, 2018.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your August 26, 2018, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific deviations including, but not limited to, the following.

1. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.

Valsartan API

Your firm received a complaint from a customer on June 6, 2018, after an unknown peak was detected during residual solvents testing for valsartan API manufactured at your facility. The unknown peak was identified as the probable human carcinogen N-nitrosodimethylamine (NDMA). Your investigation (DCE-18001) determined that the presence of NDMA was caused by the convergence of three process-related factors, one factor being the use of the solvent dimethylformamide (DMF). Your investigation concluded that only one valsartan manufacturing

February 8, 2023

EXHIBIT
AFNAN

004

process (referred to as the ZnCl_2 process in your investigation) was impacted by the presence of NDMA.

However, FDA analyses of samples of your API, and finished drug product manufactured with your API, identified NDMA in multiple batches manufactured with a different process, namely the triethylamine process, which did not use the solvent DMF. These data demonstrate that your investigation was inadequate and failed to resolve the control and presence of NDMA in valsartan API distributed to customers. Your investigation also failed:

- To include other factors that may have contributed to the presence of NDMA. For example, your investigation lacked a comprehensive evaluation of all raw materials used during manufacturing, including potable water.
- To assess factors that could put your API at risk for NDMA cross-contamination, including batch blending, solvent recovery and re-use, shared production lines, and cleaning procedures.
- To evaluate the potential for other mutagenic impurities to form in your products.

Our investigators also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms. For example, valsartan intermediates (C20213-17-339 and C20213-17-340) failed testing for an unknown impurity (specification $\leq 0.5\%$) with results of 0.56% for both batches. Your action plan indicated that the impurity would be identified as part of the investigation; however, you failed to do this. In addition, no root cause was determined for the presence of the unknown impurity. You stated that you reprocessed the batches and released them for further production.

Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was suspected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further. Additionally, residual solvent chromatograms for valsartan API validation batches manufactured using your ZnCl_2 process, with DMF in 2012 (C5355-12-001, C5355-12-002, and C5355-12-003) show at least one unidentified peak eluting after the toluene peak in the area where the presence of NDMA was suspected to elute.

Your response also states that you were not the only firm to identify NDMA in valsartan API. In your case, FDA analyses of samples identified amounts of NDMA in valsartan API manufactured at your firm that were significantly higher than the NDMA levels in valsartan API manufactured by other firms. FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation.

In response to this letter:

- Submit risk assessments for all APIs and intermediates manufactured at your facility for the potential presence of mutagenic impurities.
- Provide an update on investigations and CAPA plans initiated to address the presence of NDMA and other potential mutagenic impurities in all APIs manufactured at your firm.
- Provide a thorough, independent assessment of your overall system for investigating deviations, discrepancies, out-of-specification (OOS) results, complaints, and other failures. In addition, provide a retrospective review of all distributed batches within expiry to determine if your firm released batches that did not conform to established specifications or appropriate manufacturing standards.
- Provide test results for all angiotensin II receptor blockers (ARBs) and intermediates for the presence of NDMA, N-Nitrosodiethylamine (NDEA), and other potentially mutagenic impurities.

Levetiracetam API

Your firm received a customer complaint on September 13, 2016, concerning levetiracetam API batches (C5152-16-243 and C5152-16-254) that exceeded the specification for ethyl carbamate (≤ 0.24 ppm). Ethyl carbamate has been classified as a probable human carcinogen. Your customer's test results conflicted with your ethyl carbamate test results, which showed the two batches meeting the specification upon release. Your complaint investigation (CC-16008) identified no clear laboratory error, and no anomalies were detected during the production of the batches. Your investigation failed to evaluate other levetiracetam API batches to determine if the presence of excess ethyl carbamate was an adverse trend. For example, levetiracetam batches C5152-16-244, C5152-16-250, and C5152-16-251 were OOS for ethyl carbamate because of production errors; however, they were not discussed in your complaint investigation.

Your response states that levetiracetam API batches C5152-16-243 and C5152-16-254 were returned, reprocessed, and released to customers in non-U.S. markets.

Your response also states that in August 2017 you implemented a new ethyl carbamate test method that uses a triple quadrupole LC-MS/MS method, to replace the single quadrupole LC-MS method that was prone to erroneous OOS results. You failed to verify the reliability of the ethyl carbamate results for all levetiracetam API batches (including levetiracetam batch C5152-16-254) originally released using your single quadrupole LC-MS method, which you indicated was inferior to your updated method.

In response to this letter, provide:

- A risk assessment for all levetiracetam API batches manufactured within expiry.
- A revised complaint handling procedure and details of any further controls your facility has implemented to ensure that all complaints are adequately documented and thoroughly investigated.

- Procedures for accepting and reprocessing returned drugs.
- Results of ethyl carbamate testing of all levetiracetam API batches released to the U.S. market using your updated triple quadrupole LC-MS/MS ethyl carbamate test method.

2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.

In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce.

Your response does not describe sufficient corrective actions to ensure that your firm has adequate change management procedures in place: (1) to thoroughly evaluate your API manufacturing processes, including changes to those processes; and (2) to detect any unsafe impurities, including potentially mutagenic impurities. For FDA's current thinking on control of potentially mutagenic impurities, see FDA's guidance document *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* for approaches that FDA considers appropriate for evaluating mutagenic impurities, at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf>.

In response to this letter, provide:

- Detailed revised change management procedures describing how your firm will assess and control all impurities, including mutagenic impurities, in API and intermediates manufactured at your facility.

- Detailed procedures describing how your firm establishes impurity profiles for products manufactured at your firm. These procedures should contain instructions for comparing at appropriate intervals against the impurity profile in the regulatory submission, or for comparing against historical data, to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.
- A retrospective analysis of other API and intermediates manufactured at your firm to determine if they were adequately evaluated for anticipated and unanticipated impurities, including potentially mutagenic impurities.

CGMP consultant recommended

Based upon the nature of the deviations we identified at your firm, we strongly recommend engaging a consultant qualified to evaluate your operations and assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Quality Systems Guidance

Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidances: *Q8(R2) Pharmaceutical Development*, at <https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf>; *Q9 Quality Risk Management*, at <https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf>; and *Q10 Pharmaceutical Quality System*, at <https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf>.

Additional API CGMP guidance

FDA considers the expectations outlined in ICH Q7 in determining whether API are manufactured in conformance with CGMP. See FDA's guidance document *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* for guidance regarding CGMP for the manufacture of API, at <https://www.fda.gov/downloads/Drugs/.../Guidances/ucm073497.pdf>.

Conclusion

Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what

actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

FDA placed your firm on Import Alert 66-40 on September 28, 2018.

Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these deviations may also result in FDA continuing to refuse admission of articles manufactured at Zhejiang Huahai Pharmaceutical Co., Ltd., located at Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai Fifth Avenue, Linhai, Taizhou Zhejiang, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your deviations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Rory K. Geyer
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4235
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3003885745.

Sincerely,



Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

Exhibit 12

Exhibit 1

1 IN THE UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF NEW JERSEY
3 CAMDEN VICINAGE

4 *****
5 IN RE: VALSARTAN, LOSARTAN, MDL No. 2875
6 AND IRBESARTAN PRODUCTS
7 LIABILITY LITIGATION
8 ***** HON ROBERT B.
9 THIS DOCUMENT APPLIES TO ALL KUGLER
10 CASES
11 *****

12 - CONFIDENTIAL INFORMATION -
13 SUBJECT TO PROTECTIVE ORDER

14 Remote Videotaped Deposition of
15 DAVID L. CHESNEY, commencing at 9:40 a.m., on
16 the 21st of March, 2022, before Maureen
17 O'Connor Pollard, Registered Diplomate
18 Reporter, Realtime Systems Administrator,
19 Certified Shorthand Reporter.

20 - - -

21 GOLKOW LITIGATION SERVICES
22 877.370.3377 ph | 917.591.5672 fax
23 deps@golkow.com
24

<p style="text-align: right;">Page 2</p> <p>1 REMOTE APPEARANCES:</p> <p>2 MAZIE SLATER KATZ & FREEMAN, LLC</p> <p>3 BY: ADAM SLATER, ESQ.</p> <p>4 BY: JULIA S. SLATER, ESQ.</p> <p>5 BY: CHRISTOPHER GEDDIS, ESQ.</p> <p>6 103 Eisenhower Parkway</p> <p>7 Roseland, New Jersey 07068</p> <p>8 973-228-9898</p> <p>9 aslater@mazieslater.com</p> <p>10 cgeddis@mazieslater.com</p> <p>11 Representing the Plaintiffs</p> <p>12 RIVERO MESTRE LLP</p> <p>13 BY: JORGE MESTRE, ESQ.</p> <p>14 BY: ZALMAN KASS, ESQ.</p> <p>15 2525 Ponce De Leon Boulevard</p> <p>16 Miami, Florida 33134</p> <p>17 305-445-2500</p> <p>18 Representing the Plaintiffs</p> <p>19 GREENBERG TRAURIG LLP</p> <p>20 BY: KATE M. WITTLAKE, ESQ.</p> <p>21 4 Embarcadero Center, Suite 3000</p> <p>22 San Francisco, California 94111</p> <p>23 415-655-1285</p> <p>24 wittlakek@gtlaw.com</p> <p>Representing the Defendants Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals SA, Inc., Actavis LLC, and Actavis Pharma, Inc.</p> <p>GREENBERG TRAURIG, LLP</p> <p>BY: STEVEN M. HARKINS, ESQ.</p> <p>Terminus 200</p> <p>3333 Piedmont Road NE</p> <p>Suite 2500</p> <p>Atlanta, Georgia 30305</p> <p>678-553-2100</p> <p>harkinss@gtlaw.com</p> <p>Representing the Defendants Teva Pharmaceutical Industries, Ltd., Teva Pharmaceuticals SA, Inc., Actavis LLC,</p>	<p style="text-align: right;">Page 4</p> <p>1 APPEARANCES (Continued):</p> <p>2 FALKENBERG IVES, LLP</p> <p>3 BY: MEGAN A. ZMICK, ESQ.</p> <p>4 230 W. Monroe Street, Suite 2220</p> <p>5 Chicago, Illinois 60606</p> <p>6 312-566-4808</p> <p>7 maz@falkenbergives.com</p> <p>8 Representing the Defendant Humana</p> <p>9 BUCHANAN INGERSOLL & ROONEY PC</p> <p>10 BY: ASHLEY D.N. JONES, ESQ.</p> <p>11 BY: DEBORAH HOPE, ESQ.</p> <p>12 1700 K Street NW, Suite 300</p> <p>13 Washington, DC 20006-3807</p> <p>14 202-452-7318</p> <p>15 ashley.jones@bipc.com</p> <p>16 Representing the Defendant Albertsons</p> <p>17 LLC</p> <p>18 Videographer: David Stone</p>
<p style="text-align: right;">Page 3</p> <p>1 APPEARANCES (Continued):</p> <p>2 WALSH PIZZI O'REILLY LLP</p> <p>3 BY: CHRISTINE I. GANNON, ESQ.</p> <p>4 By: LIZA WALSH, ESQ.</p> <p>5 Three Gateway Center</p> <p>6 100 Mulberry Street, 15th Floor</p> <p>7 Newark, New Jersey 07102</p> <p>8 973-757-1017</p> <p>9 Representing the Defendants Teva</p> <p>10 Pharmaceutical Industries, Ltd., Teva</p> <p>11 Pharmaceuticals SA, Inc., Actavis LLC,</p> <p>12 and Actavis Pharma, Inc.</p> <p>13 SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP</p> <p>14 BY: THOMAS E. FOX, ESQ.</p> <p>15 One Manhattan West</p> <p>16 New York, New York 10001-8602</p> <p>17 212-735-2165</p> <p>18 thomas.fox@skadden.com</p> <p>19 Representing the Defendants Zhejiang</p> <p>20 Huahai Pharmaceutical Co., Ltd.,</p> <p>21 Princeton Pharmaceutical Inc., Huahai</p> <p>22 U.S., Inc., and Solco Healthcare US,</p> <p>23 LLC</p> <p>24 HINSHAW & CULBERTSON, LLP</p> <p>BY: GEOFFREY M. COAN, ESEQ.</p> <p>53 State Street</p> <p>Boston, Massachusetts 02109</p> <p>617-213-7047</p> <p>gcoan@hinshawlaw.com</p> <p>Representing the Defendant SciGen Pharmaceuticals</p> <p>BARNES & THORNBURG, LLP</p> <p>BY: MITCHELL CHARCHALIS, ESQ.</p> <p>2029 Century Park E, Suite 300</p> <p>Los Angeles, California 90067</p> <p>310-284-3896</p> <p>mcharchalis@btlaw.com</p> <p>Representing the Defendants CVS Pharmacy, Inc., and Rite Aid Corporation</p>	<p style="text-align: right;">Page 5</p> <p>1 INDEX</p> <p>2 EXAMINATION PAGE</p> <p>3 DAVID L. CHESNEY 10</p> <p>4 BY MR. SLATER 276</p> <p>5 BY MR. FOX 311</p> <p>6 BY MR. SLATER 348</p> <p>7 BY MR. FOX</p> <p>8</p> <p>9</p> <p>10 EXHIBITS</p> <p>11 NO. DESCRIPTION PAGE</p> <p>12 1 Notice to Take Videotaped Deposition..... 13</p> <p>13</p> <p>14 2 ZHP Defendants' Response and Objections to Notice to Take Videotaped Oral Deposition of David Chesney..... 14</p> <p>15</p> <p>16</p> <p>17 3 DL Chesney Consulting, LLC Invoices..... 15</p> <p>18 4 Expert Report of David L. Chesney, MSJ..... 24</p> <p>19</p> <p>20 5 IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, May 1978..... 116</p> <p>21</p> <p>22</p> <p>23 6 Document titled Purification of Laboratory Chemicals..... 122</p> <p>24</p>

Page 6	Page 8
<p>1</p> <p>2 7 Article in Tetrahedron, N,N-Dimethylformamide: Much more than a solvent.. 128</p> <p>3</p> <p>4 8 Sun, et al, Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine..... 131</p> <p>5</p> <p>6 9 PowerPoint titled Advanced analytical Technology Center (CEmat) Introduction..... 201</p> <p>7</p> <p>8</p> <p>9</p> <p>10 10 E-mail titled Notice on the Results of the Report of the Preliminary Investigation on the Formation of Unknown Impurities Resulting from the Sodium Azide Quenching in Crude Irbesartan, Bates ZHP00190573 and 574..... 207</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16 11 PowerPoint titled Quality Management Essentials, Expert Advice on Building a Compliant System..... 233</p> <p>17</p> <p>18</p> <p>19 12 Deviation Report Form, Bates ZHP00004352 through 4471..... 266</p> <p>20</p> <p>21 13 November 29, 2018 Warning Letter, Bates ZHP01344159 through 4164.. 320</p> <p>22</p> <p>23 14 Investigation Report, Bates ZHP00662283 through 2309..... 336</p> <p>24</p>	<p>1</p> <p>2 - - - DEPOSITION SUPPORT INDEX - - -</p> <p>3</p> <p>4 Direction to Witness Not to Answer PAGE LINE None.</p> <p>5</p> <p>6</p> <p>7</p> <p>8 Request for Production of Documents PAGE LINE None.</p> <p>9</p> <p>10</p> <p>11</p> <p>12 Stipulations PAGE LINE None.</p> <p>13</p> <p>14</p> <p>15 Questions Marked Highly Confidential PAGE LINE None.</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>
Page 7	Page 9
<p>1</p> <p>2 15 August 26, 2018 Response to FDA Inspection on July 23 - August 3, 2018, Bates ZHP02115600 through 5603..... 338</p> <p>3</p> <p>4</p> <p>5 16 Establishment Inspection Report, Bates PRINSTON00162349 through 2406..... 344</p> <p>6</p> <p>7 Defendant 1 January 25, 2019 FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues..... 291</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12 Defendant 2 August 30, 2018 FDA Statement on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings..... 297</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p>1</p> <p>2</p> <p>3</p> <p>4</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>

Page 10

1 MR. SLATER: Adam Slater, Chris
 2 Gaddis, Julia Slater for plaintiffs.
 3 MR. FOX: Thomas Fox, Skadden,
 4 Arps, for the ZHP defendants.
 5 ///

6 DAVID L. CHESNEY,
 7 having been duly remotely identified and
 8 sworn, was examined and testified as follows:
 9 EXAMINATION
 10 BY MR. SLATER:
 11 Q. Good morning, Mr. Chesney.
 12 A. Good morning.
 13 MR. FOX: Adam, I just want to
 14 make clear, this is being taken
 15 pursuant to the remote deposition
 16 protocol in the case?
 17 MR. SLATER: I think that we
 18 have a remote deposition protocol.
 19 MR. FOX: Yes.
 20 MR. SLATER: Why are you asking
 21 me that?
 22 MR. FOX: I just wanted to make
 23 sure, that's all.
 24 MR. SLATER: I just have never

Page 11

1 been asked that question before in one
 2 of depositions we were doing remotely.
 3 I thought it was a trick question. I
 4 think so.
 5 BY MR. SLATER:
 6 Q. Okay. Good morning,
 7 Mr. Chesney.
 8 A. Good morning.
 9 Q. We're going to take your
 10 deposition now. You understand that, right?
 11 A. I do.
 12 Q. Have you been deposed before?
 13 A. Yes.
 14 Q. How many times?
 15 A. Let's see. Four or five times,
 16 I guess.
 17 Q. You understand you're under
 18 oath and must tell the truth, right?
 19 A. Yes.
 20 Q. If I ask you a question that
 21 for some reason you don't feel you can answer
 22 truthfully and completely, for any reason,
 23 just tell me. It may be that I mispronounce
 24 a word, or ask you a question that

Page 12

1 technically doesn't make sense to you because
 2 I don't understand something either from a
 3 regulatory perspective or legal perspective,
 4 whatever it may be, for any reason you're not
 5 clear on my question or don't feel like you
 6 can answer it, just tell me and we'll try to
 7 figure out what I need to clarify, and I'll
 8 try to do that. Okay?
 9 A. Okay.
 10 Q. Counsel may object. I think it
 11 would be unlikely he won't object during the
 12 course of the deposition. That's routine.
 13 It's never to signal an answer or how to
 14 answer, it's just preserving rights -- or at
 15 least it should never be to signal an answer,
 16 and I doubt it would be today, and I would
 17 expect it wouldn't be.
 18 In any event, let your counsel
 19 object, and then answer the question, unless
 20 he tells you not to. Okay?
 21 A. Yes, sir.
 22 MR. SLATER: Chris, let's put
 23 up the deposition notice as Exhibit 1.
 24 ///

Page 13

1 (Whereupon, Chesney Exhibit
 2 Number 1 was marked for
 3 identification.)
 4 BY MR. SLATER:
 5 Q. Mr. Chesney, this is the
 6 deposition notice we served for your
 7 deposition.
 8 Have you seen this document
 9 before?
 10 A. Yes.
 11 Q. Did you read it and go through
 12 all the requests?
 13 A. Yes.
 14 Q. Did you provide any documents
 15 to the lawyers that retained you in this case
 16 to be provided to us pursuant to this
 17 deposition notice?
 18 A. Before I received the notice I
 19 did, yes.
 20 Q. Okay. Once you got the notice,
 21 was there anything else that you identified
 22 and provided to counsel?
 23 A. I don't recall that I did, no.
 24 Q. When you say you don't recall,

Page 14

1 you don't recall if that happened, or you
2 don't -- I'm unclear on your answer.
3 A. We had a discussion. The list
4 of requests was quite broad, and I had
5 difficulty interpreting the scope of some of
6 the requests, and we discussed that.
7 At the end of that discussion,
8 I believe counsel was going to submit a
9 response, and I never heard anything further
10 after that.
11 Q. At the end of that discussion
12 when counsel worked through what the
13 deposition notice was asking for, was there
14 any information or documents that you
15 provided to counsel to be provided to us?
16 A. No.
17 MR. SLATER: Okay. Let's take
18 that document down, and put up as
19 Exhibit 2 the response to the
20 deposition notice, please.
21 (Whereupon, Chesney Exhibit
22 Number 2 was marked for
23 identification.)
24 ///

Page 15

1 BY MR. SLATER:
2 Q. On the screen as Exhibit 2 is
3 what we were provided as the response to our
4 deposition notice. Have you seen that
5 document?
6 A. No.
7 Q. One of the things we requested
8 from you was the invoices in this matter.
9 MR. SLATER: And I guess,
10 Chris, let's go to the invoices as
11 Exhibit 3, and then we'll come back to
12 the dep notice after, if that's
13 possible.
14 (Whereupon, Chesney Exhibit
15 Number 3 was marked for
16 identification.)
17 MR. SLATER: Perfect. Thank
18 you.
19 BY MR. SLATER:
20 Q. On the screen as Exhibit 3 are
21 the invoices we were provided, and it shows
22 that you began to work in this matter in June
23 of 2021, is that correct?
24 A. That's correct.

Page 16

1 Q. Who contacted you and asked you
2 to get involved in this case?
3 A. Frederick Ball of Duane Morris.
4 Q. Did you know Mr. Ball before he
5 contacted you in June of 2021?
6 A. No.
7 Q. You'd never met him before?
8 A. I had not.
9 Q. Do you know how it was that he
10 came to contact you? Did he tell you why he
11 contacted you?
12 A. I don't recall. He probably
13 told me at the time, but I don't recall now
14 where he got my name.
15 Q. The response to the deposition
16 notice, which we don't have to pull up, says
17 that the invoices that were provided were in
18 connection with the preparation of your
19 expert report and your related testimony in
20 this litigation. Is that what these invoices
21 represent?
22 A. Yes. The majority of the time
23 was the preparation of the expert report and
24 the work I did researching information in

Page 17

1 that preparation.
2 Q. Other than writing this report
3 and preparing for this deposition, have you
4 done any other work for ZHP or any of its
5 subsidiaries in connection with the
6 nitrosamine contamination of its valsartan?
7 A. No.
8 Q. Have you been asked to consult
9 or provide any opinions with regard to any
10 disputes that ZHP may be having with any of
11 its customers?
12 A. No.
13 Q. Okay. I added up these
14 invoices which are dated between June 2021
15 and January of 2022 at \$51,000.
16 Does that sound correct?
17 A. I think it's a little on the
18 low side. I had added them up, and I think I
19 came up with around 56.
20 Q. Okay. These invoices are up
21 through January of 2022, the last one being
22 \$13,000.
23 MR. SLATER: Maybe we can go to
24 that one, Chris, the last page.

Page 18

1 Perfect.

2 Q. Looking at the last page of

3 this group of invoices, this is from January

4 of 2022, \$13,000, correct?

5 A. Yes.

6 Q. What amount of time have you

7 spent since January up until today in

8 connection with this matter?

9 A. I have that information on my

10 time sheet records, but I don't have it with

11 me. It's approximately 25 hours, more or

12 less.

13 Q. Does that include your

14 preparation right up until the point when we

15 started the deposition?

16 A. I don't believe it includes the

17 hours I spent this weekend looking over my

18 report, but it's pretty close. It might be

19 between 25 and 30.

20 Q. So 25 hours approximately

21 before the weekend, and then maybe another

22 five or so hours over the weekend before

23 today's deposition?

24 A. Approximately, yes.

Page 19

1 Q. Okay. Thank you.

2 MR. SLATER: All right. Chris,

3 let's go back to the deposition

4 notice, if we could, please. Not the

5 notice, I'm sorry, I meant the

6 response. My bad. Thank you.

7 Q. I'm not going to go through all

8 these requests, and you haven't read the

9 responses, so I'm not going to go through

10 that with you today in great detail. But

11 what I would like to ask you is --

12 MR. SLATER: Let's go to

13 request number 8. That's the -- go to

14 the responses and objections to the

15 requests, number 8. Perfect. Thanks,

16 Chris.

17 Q. Looking at number 8, which we

18 asked for any documentation of any research

19 that you had performed with regard to the

20 FDA's regulation of API and finished drug

21 products, FDA inspections, current good

22 manufacturing processes, and the risks and

23 benefits of any angiotensin II receptor

24 blockers or nitrosamines, we were told that

Page 20

1 you had worked at the FDA for 23 years, and

2 have had an FDA-related consulting practice

3 for more than a quarter of a century, and in

4 those roles you'd informally researched

5 countless issues over the course of your

6 career, and that you have already submitted a

7 list of your publications, and not conducted

8 academic research regarding the list of

9 topics. That was the response we were given.

10 You can see that there.

11 Do you see that?

12 A. Yes.

13 Q. I just want to know talking to

14 you now, have you in connection with this

15 work -- well, rephrase.

16 Have you ever done any research

17 regarding nitrosamines?

18 A. No.

19 Q. And that's true right up until

20 right now?

21 A. Other than just briefing myself

22 on the general issue and rereading some of

23 the press that was out when it was made

24 public and that sort of thing. No, no

Page 21

1 technical research.

2 Q. I think I saw in a few places

3 in your report where you said you'd defer to

4 scientific or to others with scientific

5 expertise.

6 Is this one of the areas where

7 you would defer to others with scientific

8 expertise, meaning the nitrosamines and the

9 risks posed by nitrosamines?

10 A. Yes.

11 MR. FOX: Objection to form.

12 Just make sure you slow down,

13 David, so you give me an opportunity

14 to make an objection on the record.

15 BY MR. SLATER:

16 Q. I'll just ask it again just

17 because counsel objected, it may be that I

18 talked too much in my question, happens from

19 time to time.

20 Am I correct that you'd defer

21 to other experts regarding the risks posed by

22 nitrosamines as relevant in this case?

23 A. Yes.

24 Q. When I asked you if you'd defer

Page 22

1 to others, I didn't see you specifically cite
 2 any of their expert reports, you're just
 3 saying in general you would defer to others
 4 who have that expertise, is that correct?
 5 MR. FOX: Objection to the
 6 form.
 7 A. Yes.
 8 BY MR. SLATER:
 9 Q. Am I correct that in your
 10 experience both with the FDA and as a
 11 consultant following the time you left the
 12 FDA, you've never been involved in a matter
 13 that involved potential nitrosamine
 14 impurities in either an API or a finished
 15 dose product?
 16 A. That's correct.
 17 Q. Is this the first time in your
 18 career you've been involved in a matter where
 19 nitrosamines were a relevant factor in the
 20 analysis you were providing, meaning one of
 21 the constituent variables in the case was
 22 nitrosamines?
 23 MR. FOX: Objection to form.
 24 A. Yes.

Page 23

1 BY MR. SLATER:
 2 Q. Before you were retained in
 3 this case, had you ever heard of NDMA?
 4 A. Yes.
 5 Q. And how did you know what NDMA
 6 was?
 7 A. There were press reports
 8 involving the occurrence of NDMA in a variety
 9 of products, some gastrointestinal products
 10 as well as the valsartan-irbesartan family,
 11 and I read those press reports in the
 12 literature.
 13 Q. Other than seeing press reports
 14 regarding the recent discovery of NDMA in
 15 various drug products, had you ever had any
 16 occasion to know what NDMA was before that?
 17 A. No.
 18 MR. FOX: Objection to form.
 19 Slow down, David.
 20 BY MR. SLATER:
 21 Q. I didn't see any discussion of
 22 NDEA in your report. Is that something you
 23 did not address at all in your report?
 24 A. I did not address it.

Page 24

1 Q. I also saw no discussion of the
 2 TEA process for manufacture of valsartan API
 3 at ZHP. Am I also correct that is not
 4 something that you addressed at all in your
 5 report?
 6 A. You're correct.
 7 MR. SLATER: Let's take those
 8 down and go to Mr. Chesney's report.
 9 We'll mark that as Exhibit 3, along
 10 with the attached Exhibits A and B.
 11 (Whereupon, Chesney Exhibit
 12 Number 4 was marked for
 13 identification.)
 14 BY MR. SLATER:
 15 Q. Mr. Chesney, you have in front
 16 of you on the screen your report which we've
 17 marked as Exhibit 3. I understand you're not
 18 scrolling right through it, but does that
 19 look like the first page of your report?
 20 A. Yes.
 21 Q. And I can tell you --
 22 MR. GEDDIS: Adam, for the
 23 record it's Exhibit 4.
 24 MR. SLATER: Did I say 3? I

Page 25

1 meant 4. Sorry about that. Let me
 2 rephrase.
 3 BY MR. SLATER:
 4 Q. Mr. Chesney, on the screen as
 5 Exhibit 4 we have your report. Does that
 6 look like your report right there?
 7 A. Yes.
 8 Q. And I have it as 59 pages, and
 9 then there's a digital signature for you on,
 10 it looks like, January 12, 2022. Is that
 11 when you put your signature on it and stamped
 12 this as a final report?
 13 A. I'm not looking at it, but that
 14 sounds right.
 15 Q. Do you have your report there
 16 in hard copy?
 17 A. I do. I was just trying to
 18 flip to that page.
 19 Q. Go ahead, take a look, and
 20 we'll just make sure we're on the same page
 21 of that.
 22 MR. SLATER: You don't have to
 23 scroll to that, I don't think, Chris,
 24 because he has it.

Page 26

1 A. Yes, it was digitally signed on
2 January 12th, that's correct.
3 Q. And that was the day when you
4 finalized and confirmed your opinions in this
5 case?
6 A. Yes.
7 Q. Does this report contain each
8 of the opinions you formed in this matter?
9 A. Yes.
10 Q. You went through a number of
11 facts and discussed a number of facts in the
12 course of your report. Were those the facts
13 that you felt were most important to you in
14 supporting or formulating your opinions?
15 A. Yes.
16 MR. FOX: Objection to form.
17 BY MR. SLATER:
18 Q. I'm just going to digress for a
19 second. We can leave that on the screen. I
20 just want to ask you a few background
21 questions.
22 Can you tell me how many times
23 you've been retained as an expert witness in
24 civil litigation?

Page 27

1 A. Four or five times.
2 Q. What is the bulk of the work
3 you have done as a consultant since you left
4 the FDA? It sounds like it's not
5 litigation-based, so I'm curious what it is
6 that you generally do.
7 A. I provide advice to clients on
8 compliance strategy. I help them respond to
9 FDA findings when they have inspections. I
10 help them prepare for and manage FDA
11 inspections. I conduct audits from time to
12 time, some of which are general audits for
13 compliance purposes, others of which are
14 intended as mock FDA inspections to help them
15 prepare for the real event. Any of a variety
16 of other ad hoc issues that arise with
17 clients that involve FDA compliance matters.
18 Q. Have you ever done any work in
19 the past for ZHP, Princeton, Solco, or Huahai
20 US?
21 A. No.
22 Q. Have you done any work for any
23 of the other manufacturers or parties to this
24 litigation, to your knowledge?

Page 28

1 A. The only two I recall seeing
2 the names of are Teva and Mylan, and the
3 answer in both cases is no.
4 Q. How about Aurobindo?
5 A. No.
6 Q. Hetero?
7 A. No.
8 Q. How about Torrent?
9 A. No.
10 Q. When you were an FDA
11 investigator -- rephrase.
12 When you worked at the FDA, did
13 your responsibilities include evaluation of
14 manufacturers to determine whether there were
15 GMP violations in the manufacture of API?
16 A. Yes.
17 Q. Same question with regard to
18 manufacture of finished dose products.
19 A. Yes.
20 Q. In your work at the FDA, how
21 much of your work was focused on that area,
22 evaluation of potential GMP violations in the
23 manufacture of API or finished dose?
24 A. I can't quantitate that

Page 29

1 precisely for you.
2 Q. Can you give me some idea of
3 how many matters you investigated where that
4 was the question?
5 MR. FOX: Objection to form.
6 A. Almost impossible, sir. I
7 began my FDA career in 1972. Between that
8 and my consulting career, I've spent nearly
9 50 years. It's very difficult to say how
10 many of these issues I've dealt with over an
11 extensive period of time like that.
12 BY MR. SLATER:
13 Q. So -- and I'm not going to push
14 it. If you're not able to estimate the
15 number of times that you addressed that issue
16 at the FDA, I'll let it go if you tell me
17 that.
18 A. I could not give you an
19 estimate I would be confident about.
20 Q. Looking at your report, let me
21 just find a good jumping off point.
22 MR. SLATER: Let's go to
23 page 11, if we could, please, Chris.
24 Q. I was curious, on page 11 --

Page 30

1 rephrase.
2 On page 11 there's a heading
3 "FDA Awards and Recognition" --
4 A. Yes.
5 Q. -- that says, "In 1990, I
6 received the FDA Award of Merit, the FDA's
7 highest award for individual achievement, for
8 my work coordinating a major investigation
9 involving deliberate contamination of
10 imported produce sent to the United States."
11 When you say "deliberate
12 contamination," what was that referring to?
13 What happened?
14 A. Injection of grapes from a
15 country of Chile with cyanide residues.
16 Q. I suppose you would agree with
17 me that the deliberate contamination of a
18 product regulated by the FDA would be a
19 significant violation?
20 MR. FOX: Objection to form.
21 A. Yes.
22 BY MR. SLATER:
23 Q. Would you agree that the
24 deliberate contamination of a product

Page 31

1 regulated by the FDA would be a GMP
2 violation?
3 MR. FOX: Objection to form.
4 A. It depends.
5 BY MR. SLATER:
6 Q. Well, in this case where
7 somebody injected cyanide into grapes, was
8 that a GMP violation?
9 A. No.
10 Q. What was it a violation of?
11 A. Title 18 US Code Section 1365
12 of the Federal Anti-Tampering Act.
13 Q. If the grapes had been injected
14 by somebody unrelated to the seller who was
15 ultimately the target of your investigation,
16 but the seller knew that they had been
17 injected and still went ahead and shipped the
18 grapes, would that be a violation?
19 MR. FOX: Objection to the
20 form.
21 A. Yes, of course.
22 BY MR. SLATER:
23 Q. What would that be a violation
24 of?

Page 32

1 A. Well, that could be a violation
2 of the Food, Drug and Cosmetic Act if they
3 knowingly shipped a product that they knew to
4 be contaminated.
5 Q. If ZHP knowingly sold valsartan
6 and knew that it had NDMA in it, would that
7 be a violation of the -- of any regulations
8 or laws?
9 MR. FOX: Objection to form.
10 No foundation.
11 A. That depends.
12 BY MR. SLATER:
13 Q. If before FDA dis -- rephrase.
14 If before ZHP disclosed to the
15 FDA that there was NDMA in its valsartan, if
16 ZHP had been selling the valsartan for a
17 period of time knowing that anyway and it
18 still sold the product, would that have been
19 a violation?
20 MR. FOX: Objection to form.
21 No foundation.
22 A. It depends.
23 BY MR. SLATER:
24 Q. Depends on what?

Page 33

1 A. Depends on the levels of NDMA,
2 what was known about it, whether they posed a
3 hazard to people who might ingest the
4 product. A variety of factors.
5 Q. So you're not able to form an
6 opinion based on my question?
7 A. Not based on your question.
8 Q. Okay. If we go to page 12 of
9 your report, the last matter listed is
10 October 2021 and continuing, a "Contractual
11 dispute between two pharmaceutical companies
12 over cost recovery from a recall alleged to
13 have been necessitated by GMP deviations at
14 the contractor."
15 Can you tell me the name of
16 that matter?
17 MR. FOX: It's subject to a
18 confidentiality order. But, David,
19 you can tell him the name of the
20 matter.
21 THE WITNESS: Okay.
22 [REDACTED]
[REDACTED]
[REDACTED]

Page 34

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]
14 [REDACTED]
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 [REDACTED]

Page 35

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 Q. Good manufacturing practices
8 requires a manufacturer to recognize
9 potential creation of impurities so that they
10 can be assessed, correct?
11 MR. FOX: Objection to form.
12 A. If information comes to light
13 that raises that suspicion, GMP would require
14 that it be looked into.
15 MR. SLATER: Chris, go to
16 Exhibit A of Mr. Chesney's report,
17 please.
18 Q. Mr. Chesney, Exhibit A to your
19 report is your CV. Is that your up-to-date
20 CV?
21 A. It is.
22 Q. Have you ever given any
23 presentations as a consultant -- rephrase.
24 After you left the FDA, did you
ever give any presentations regarding the

Page 36

1 application of GMP to the manufacture of API
2 or finished dose?
3 A. Not as the sole subject in the
4 presentation.
5 Q. But that's something that's
6 come up as part of some presentations?
7 A. Yes.
8 Q. Do you have those presentations
9 still?
10 A. Some.
11 Q. Have you given any
12 presentations -- rephrase.
13 Since the time you left the
14 FDA, have you given any presentations
15 regarding what a GMP-compliant risk
16 assessment for a drug manufacturing process,
17 whether API or finished dose, would involve?
18 MR. FOX: Objection to form.
19 A. Not as the sole subject of a
20 presentation.
21 BY MR. SLATER:
22 Q. But again, something that's
23 come up in the course of some presentations?
24 A. Yes.

Page 37

1 Q. Are those presentations you
2 still have?
3 A. Some.
4 Q. When you were at the FDA, did
5 you give any presentations regarding what GMP
6 required in terms of a risk assessment in
7 connection with the manufacturing process for
8 API or finished drug?
9 A. No.
10 Q. When you were at the FDA, did
11 you ever write any reports or sign off on any
12 reports addressing whether or not there was a
13 GMP violation in connection with the risk
14 assessment for a manufacturing process for
15 either API or finished drug?
16 MR. FOX: Objection to form.
17 A. Not specifically, no.
18 BY MR. SLATER:
19 Q. When you say "not
20 specifically," does that mean -- what does
21 that mean?
22 A. I reviewed and signed off on
23 many reports involving API manufacturing.
24 But in the era when I was working for the

Page 38

1 FDA, the requirements and expectations for
 2 documentation of risk assessment were not as
 3 detailed or well understood as they are
 4 today.
 5 MR. SLATER: Let's go, Chris,
 6 if we could, to Exhibit B, please.
 7 Q. And, Mr. Chesney, you're
 8 welcome to look at your hard copy report as
 9 well as I ask you questions if it's easier,
 10 whatever you think -- whatever is easiest for
 11 you. Okay?
 12 A. Thank you. I have it open
 13 here. I'll try to work off the screen. If I
 14 need to stop, I'll let you know.
 15 Q. Fair enough.
 16 Exhibit B is titled
 17 "References," and it's my understanding those
 18 are the materials that -- well, actually let
 19 me rephrase it.
 20 Exhibit B is titled
 21 "References," and there's a list of
 22 129 items. Did you read all of those items?
 23 A. I, at minimum, read them
 24 cursorily, but I didn't necessarily read

Page 39

1 every word in every item, no.
 2 Q. With regard to the -- let me
 3 start over.
 4 The first reference is the
 5 Expert Declaration of John Quick. Did you
 6 read that?
 7 A. Yes.
 8 Q. Number 2 is the Expert
 9 Declaration of Rena Conti. Did you read
 10 that?
 11 A. I did.
 12 Q. Did you find that to be
 13 relevant to the work you were doing?
 14 MR. FOX: Object to form.
 15 A. Mr. Quick's declaration, yes.
 16 Dr. Conti's was helpful from a
 17 contextual standpoint, but I don't believe I
 18 relied on it to any great extent.
 19 BY MR. SLATER:
 20 Q. She is an economist. You
 21 didn't provide any opinions regarding
 22 economics or economic damages, right?
 23 A. No, I did not.
 24 Q. Number 3 is the Plaintiffs'

Page 40

1 Memorandum of Law in Support of their Motion
 2 for Class Certification of Consumer Economic
 3 Loss Claims. Did you read that?
 4 A. Cursorily.
 5 Q. And I didn't see any opinions
 6 in your report regarding whether or not this
 7 matter was suitable or not for class
 8 certification. Am I correct that's not an
 9 issue you addressed?
 10 A. That is not an issue --
 11 MR. FOX: Objection to form.
 12 David, you have to slow up.
 13 THE WITNESS: Sorry.
 14 MR. FOX: Objection to the
 15 form.
 16 You can answer.
 17 A. That is not within my area of
 18 expertise, and I did not address it, no.
 19 BY MR. SLATER:
 20 Q. And I -- rephrase. The second
 21 -- rephrase.
 22 The next reference is reference
 23 4, Memorandum of Law in Support of the
 24 Medical Monitoring Plaintiffs' Motion for

Page 41

1 Class Certification. Did you read that?
 2 A. Again, cursorily.
 3 Q. What, if anything, about your
 4 cursory reading of those two memorandums of
 5 law was of any significance or use to you;
 6 anything?
 7 MR. FOX: Objection to the
 8 form.
 9 A. It was of use to me in
 10 understanding the context and the background,
 11 but not the details of fulfilling my remit in
 12 this matter.
 13 BY MR. SLATER:
 14 Q. Was there anything you read
 15 about in those briefs, those memorandum of
 16 laws -- memorandums of law that you said,
 17 Well, that's interesting, I should probably
 18 look at that, so -- and did you ask the
 19 lawyers, Hey, can you get me this document or
 20 that document, or this testimony or that
 21 testimony that you read about in the briefs?
 22 Did that happen at all?
 23 A. I don't recall it happening.
 24 It was months ago.

<p style="text-align: right;">Page 42</p> <p>1 Q. With regard to the materials 2 here, I can assure you we're not going to go 3 through every single one of them because that 4 would take a while, I want to ask you a few 5 general questions about the references here. 6 Did you ask for any specific 7 materials when you were engaged in this 8 matter where you said, Look, this is what you 9 have to provide me so I can formulate an 10 opinion? 11 A. I may have asked for one or two 12 items. I was provided with a great volume of 13 material. The first thing I did was try to 14 organize it, sort it out, see what was there. 15 And then as I got into the 16 details of some of the items, there were 17 things that I wanted to see that had not been 18 provided. 19 Q. What, if anything, did you ask 20 for that had not been provided to you in the 21 course of your work in this matter? 22 A. One I recall was that when ZHP 23 initiated the recall of their product, it is 24 FDA's common practice to send what's called a</p>	<p style="text-align: right;">Page 44</p> <p>1 extent you read these materials and saw 2 something that you felt to be of significance 3 you related it in your report? 4 A. Yes. 5 Q. Item number 5 on the reference 6 list is the Third Party Payors' Brief in 7 Support of Motion to Certify Class. Did you 8 read that? 9 A. I glanced at it. 10 Q. Is there anything of 11 significance about that that you can point to 12 now? 13 A. No. 14 MR. FOX: Object to the form. 15 BY MR. SLATER: 16 Q. Item number 11 is the Princeton 17 Pharmaceuticals Audit Report, dated 18 January 31, 2012, for inspection dates 19 January 31, 2012. Did you read that? 20 A. Yes. 21 Q. I don't think I saw it 22 referenced at all in your report in any 23 specificity, is that correct? 24 A. I suppose. I don't recall</p>
<p style="text-align: right;">Page 43</p> <p>1 recall classification letter. It's a 2 template letter that says the agency agrees 3 with the decision, and informs the recalling 4 company of the class FDA has assigned to the 5 recall. 6 I don't believe that was in the 7 initial package, and I did ask for that 8 document. 9 Q. Anything else that you 10 requested? 11 A. I remember that one 12 specifically. There may well have been 13 others. This was a very voluminous document 14 set, and as I went through it, if I found 15 there was something I either could not find 16 or felt I needed, then I would request it. 17 But I didn't keep a list of 18 what I asked for separately from what was 19 volunteered to me at the outset. 20 Q. You told me earlier that those 21 facts that you found to be important to you 22 in formulating your opinions were discussed 23 in your report. 24 So can I trust that to the</p>	<p style="text-align: right;">Page 45</p> <p>1 referencing it. And there are several 2 similar reports. I -- at this point by 3 memory I can't distinguish one from the 4 other. 5 Q. Do you know if you read each of 6 the audit reports or not? 7 A. I looked at all of the listed 8 reports, yes. 9 Q. And because they were not 10 discussed in any -- at all in the report, can 11 I assume that you didn't find anything to be 12 of any real significance in those reported 13 reports? 14 MR. FOX: Objection to form. 15 A. Not for the purpose I was asked 16 to fulfill. 17 BY MR. SLATER: 18 Q. What did you have an 19 understanding -- rephrase. 20 What was your understanding of 21 your role? What were you asked to opine on? 22 A. I was asked to opine on what 23 the documents in this matter caused me to 24 think of the GMP compliance status of ZHP</p>

<p>Page 46</p> <p>1 facilities.</p> <p>2 Q. Am I correct that your opinions</p> <p>3 regarding GMP were confined to ZHP and its</p> <p>4 manufacturing of the API?</p> <p>5 A. Yes.</p> <p>6 Q. I didn't see any discussion or</p> <p>7 opinions regarding Princeton, Solco, or Huahai</p> <p>8 US. Am I correct you gave no opinions</p> <p>9 regarding their actions or their compliance</p> <p>10 or noncompliance with GMP?</p> <p>11 A. That's correct.</p> <p>12 Q. I also saw no discussion of</p> <p>13 ZHP's manufacturing of the finished dose</p> <p>14 products. Am I correct that's not an issue</p> <p>15 you addressed in your report?</p> <p>16 MR. FOX: Objection to form.</p> <p>17 A. At least one of the FDA</p> <p>18 inspections touched on that, and I may have</p> <p>19 summarized some of the findings from that</p> <p>20 inspection. But I did not focus greatly on</p> <p>21 the finished dose for manufacturing issues.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. I didn't see any opinions</p> <p>24 regarding ZHP's manufacture of finished dose</p>	<p>Page 48</p> <p>1 of 2016 require that such a statement be</p> <p>2 accurate?</p> <p>3 MR. FOX: Objection to form.</p> <p>4 A. All GMP statements are required</p> <p>5 to be accurate.</p> <p>6 BY MR. SLATER:</p> <p>7 Q. And this would be a GMP</p> <p>8 statement, correct?</p> <p>9 MR. FOX: Objection to form.</p> <p>10 A. It's a statement as to the</p> <p>11 presence or absence or impact if it is</p> <p>12 present of toxic compounds in the product.</p> <p>13 It's not really a GMP statement per se.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. The genotoxicity statement</p> <p>16 whereby ZHP represented that no genotoxic</p> <p>17 impurities are present in the substance was</p> <p>18 certainly required to be a true statement if</p> <p>19 that's what they were saying, right?</p> <p>20 MR. FOX: Objection to form.</p> <p>21 A. Yes, any such statement</p> <p>22 submitted to the FDA would be required to be</p> <p>23 true, yes.</p> <p>24 ///</p>
<p>Page 47</p> <p>1 product. Is that correct, you didn't</p> <p>2 actually offer any opinions specific to that</p> <p>3 issue?</p> <p>4 A. Not that I can recall.</p> <p>5 MR. SLATER: Chris, can you go</p> <p>6 down to item number 19, please?</p> <p>7 Q. Number 19 on this list is ZHP</p> <p>8 Genotoxicity Statement, dated July 6, 2016,</p> <p>9 and it has a Torrent Bates number.</p> <p>10 Do you see that item?</p> <p>11 A. I do.</p> <p>12 Q. Is that something you read?</p> <p>13 A. If it's on the list I did, yes.</p> <p>14 Q. And I can tell you, and you can</p> <p>15 tell me if this comports with your</p> <p>16 recollection, that the genotoxicity statement</p> <p>17 is a representation that there were no</p> <p>18 genotoxic impurities in the valsartan API</p> <p>19 being sold by ZHP. Is that your</p> <p>20 understanding?</p> <p>21 MR. FOX: Objection to form.</p> <p>22 A. That is my recollection.</p> <p>23 BY MR. SLATER:</p> <p>24 Q. Did cGMP at that time in July</p>	<p>Page 49</p> <p>1 BY MR. SLATER:</p> <p>2 Q. What would be the regulatory</p> <p>3 framework within which such a statement would</p> <p>4 be evaluated, if it turned out it wasn't</p> <p>5 true?</p> <p>6 MR. FOX: Objection to form.</p> <p>7 A. I'm not sure I understand your</p> <p>8 question.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. You said that such a</p> <p>11 statement -- rephrase.</p> <p>12 You agree with me that the</p> <p>13 statement that no genotoxic impurities are</p> <p>14 present in the substance was required to be</p> <p>15 true, right?</p> <p>16 A. Yes.</p> <p>17 Q. If that statement was false,</p> <p>18 what would be the regulatory or other</p> <p>19 framework within which that would be</p> <p>20 evaluated?</p> <p>21 MR. FOX: Objection to form.</p> <p>22 A. That would depend on the</p> <p>23 purpose for the submission of the statement.</p> <p>24 ///</p>

<p>Page 50</p> <p>1 BY MR. SLATER:</p> <p>2 Q. If the statement was made to</p> <p>3 allow a downstream purchaser of ZHP's API to</p> <p>4 be confident that the API did not contain</p> <p>5 genotoxic impurities, what would be the</p> <p>6 framework for evaluating that statement?</p> <p>7 MR. FOX: Objection to form.</p> <p>8 A. First of all, whether or not it</p> <p>9 was true and accurate. And it would not be a</p> <p>10 GMP statement per se. If it were submitted</p> <p>11 to the FDA directly because the agency</p> <p>12 requested it or in connection with a pending</p> <p>13 application or something of that sort, then</p> <p>14 it would come under the regulations for new</p> <p>15 drug applications or abbreviated new drug</p> <p>16 applications.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. Any time that ZHP made a</p> <p>19 representation to the FDA as to whether or</p> <p>20 not there were genotoxic impurities in the</p> <p>21 valsartan API, that would come within the</p> <p>22 ANDA regulations, is that correct?</p> <p>23 MR. FOX: Objection to form.</p> <p>24 A. It depends on the context, but</p>	<p>Page 52</p> <p>1 requests that I may have made, yes.</p> <p>2 Q. You would agree with me that if</p> <p>3 there were material documents, meaning</p> <p>4 material -- rephrase.</p> <p>5 You would agree with me that to</p> <p>6 the extent there were documents that would be</p> <p>7 material to your formation of that opinion</p> <p>8 that were not provided to you, that could</p> <p>9 potentially be problematic, correct?</p> <p>10 MR. FOX: Objection to form.</p> <p>11 Calls for speculation.</p> <p>12 A. I'm not aware that there were</p> <p>13 any such documents. And if I felt something</p> <p>14 was needed and I didn't have it, I requested</p> <p>15 it.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. You told me about the one</p> <p>18 document you requested regarding the recall.</p> <p>19 Is there any other document you can recall</p> <p>20 that you asked for?</p> <p>21 MR. FOX: Objection. Asked and</p> <p>22 answered.</p> <p>23 A. I did a little independent</p> <p>24 research as well, looking at publicly</p>
<p>Page 51</p> <p>1 much of the time, yes.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. Any statements ZHP made to the</p> <p>4 FDA about whether or not there were genotoxic</p> <p>5 impurities in the valsartan API was required</p> <p>6 to be a true and accurate statement, correct?</p> <p>7 A. Yes.</p> <p>8 MR. FOX: Objection to form.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. You told me a few moments ago</p> <p>11 that your task in this matter was to review</p> <p>12 the documents provided to you and to evaluate</p> <p>13 the GMP compliance status of the ZHP</p> <p>14 manufacturing facility based upon your review</p> <p>15 of those documents, correct?</p> <p>16 A. Yes.</p> <p>17 MR. FOX: Objection to form.</p> <p>18 BY MR. SLATER:</p> <p>19 Q. Did you rely on the attorneys</p> <p>20 who provided those documents to you to make</p> <p>21 sure that you had all of the documents</p> <p>22 relevant to forming such an opinion?</p> <p>23 A. Between the initial information</p> <p>24 they provided and responding to subsequent</p>	<p>Page 53</p> <p>1 available data on the FDA's website regarding</p> <p>2 the compliance history of ZHP. That was not</p> <p>3 supplied by the attorneys.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Ultimately your opinion is</p> <p>6 dependent on the materials you reviewed,</p> <p>7 correct?</p> <p>8 MR. FOX: Objection to form.</p> <p>9 A. Yes.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. If I were to be able to show</p> <p>12 you documents during the course of this</p> <p>13 deposition where you would say, You know,</p> <p>14 that's a document that would have been</p> <p>15 material to me so I would have to look at</p> <p>16 that document and reevaluate my opinion, that</p> <p>17 would -- if that were to happen, that would</p> <p>18 place your opinion in question until you'd</p> <p>19 have the chance to review that document and</p> <p>20 determine whether it affected your opinion,</p> <p>21 right?</p> <p>22 MR. FOX: Objection. Calls for</p> <p>23 speculation.</p> <p>24 A. I have no way of knowing that</p>

<p style="text-align: right;">Page 54</p> <p>1 without seeing the specifics. 2 BY MR. SLATER: 3 Q. Let me talk to you -- and let 4 me be specific in what I'm asking you. 5 In terms of your approach to 6 this case, your methodology, you've already 7 told me that you relied on the documents that 8 you reviewed to form your opinion. We've 9 already gone over that. 10 What I'm getting at is, if I 11 were to show you a document or ask you about 12 a type of document and you said, Well, I 13 didn't see that, and if that existed that 14 would be important to me, something I would 15 have needed to take into account in order to 16 form my opinion in this case, if that were to 17 happen, would you agree with me that you 18 would then want to review that document and 19 then offer an opinion based on everything you 20 had seen inclusive of that document? 21 MR. FOX: Objection to form. 22 A. It would depend on the 23 specifics. 24 ///</p>	<p style="text-align: right;">Page 56</p> <p>1 relevant to the issues that you looked at, 2 you would have expected to be provided those 3 so you could take those into account in 4 forming your opinion, correct? 5 MR. FOX: Objection to form. 6 A. Yes. 7 BY MR. SLATER: 8 Q. So for example, with regard 9 to -- well, withdraw that. 10 If, in fact, there were 11 internal SOPs from ZHP that you were not 12 provided that relate, for example, to the 13 change control process or the change control 14 that was -- rephrase. 15 If there was a -- rephrase. 16 If there was an internal 17 standard operating procedure from ZHP 18 addressing the change in manufacturing 19 process, you would have wanted to see that, 20 right? 21 MR. FOX: Objection to form. 22 A. I did see one related to that. 23 BY MR. SLATER: 24 Q. Is it listed on your list of</p>
<p style="text-align: right;">Page 55</p> <p>1 BY MR. SLATER: 2 Q. One of the things that you 3 talked about in your report were internal 4 standard operating procedures which you 5 mention can go by various nomenclatures; 6 standard operating procedures, standard 7 management procedures, they can have various 8 titles, but you talked about that concept in 9 your report, right? 10 A. Yes. 11 Q. And I think -- you can correct 12 me if I'm wrong, I think what you said was 13 those internal -- and I'm going to call them 14 generically standard operating procedures or 15 SOPs, okay? 16 A. That's fine. 17 Q. I think you said in your report 18 that to the extent a company actually adopts 19 such SOPs as part of their GMP processes, 20 they're required to comply with those SOPs. 21 Did I understand that 22 correctly? 23 A. Yes. 24 Q. So if ZHP had internal SOPs</p>	<p style="text-align: right;">Page 57</p> <p>1 references? 2 A. No. 3 Q. Is it listed in your report in 4 a footnote? 5 A. Yes. 6 Q. Is that 18.01? 7 A. That's a typographical error. 8 I've discovered it should be 18.08. 9 The reason it may not be listed 10 in the references is it was an attachment to 11 the warning letter response that ZHP sent in, 12 so it was included in another item that is 13 referenced. 14 Q. Why are you saying that 18.08 15 should have been listed as opposed to 18.01? 16 A. Because I looked at it over the 17 weekend and double-checked it against the 18 footnote in my report, and found the report 19 has a typo in that number. 20 Q. So the S -- it's actually an 21 SMP. 22 A. Yes. 23 Q. Okay. So the SMP that you saw 24 was 18.08?</p>

<p style="text-align: right;">Page 58</p> <p>1 A. Yes.</p> <p>2 Q. You did not see any of the</p> <p>3 other iterations of SMP 18, correct?</p> <p>4 A. I did not, but the .08 version</p> <p>5 has a complete revision history, so I was</p> <p>6 able to tell from that what changes had been</p> <p>7 made over time.</p> <p>8 Q. As you sit here now, do you</p> <p>9 know what the form of that SMP was when the</p> <p>10 manufacturing change process was being</p> <p>11 evaluated by ZHP?</p> <p>12 MR. FOX: Objection to form.</p> <p>13 A. I'm sorry, you said the form?</p> <p>14 I don't follow your question.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. Let me ask you this. Did you</p> <p>17 ask to be shown the SMP that was actually in</p> <p>18 effect when ZHP was going through the change</p> <p>19 control process?</p> <p>20 A. By retrospectively looking at</p> <p>21 the revision history, I believe it was</p> <p>22 version 5 or version 6, I don't recall as I</p> <p>23 sit here. But I was able to see what changes</p> <p>24 had been made since then in '08, and use that</p>	<p style="text-align: right;">Page 60</p> <p>1 Whether it would be most important or not is</p> <p>2 -- I'm not prepared to say, but it certainly</p> <p>3 would be important.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Well, in terms of whether or</p> <p>6 not ZHP complied with the SMP governing</p> <p>7 change control, the version that was in</p> <p>8 effect when ZHP conducted that change control</p> <p>9 review would be the one that you would want</p> <p>10 to look to to determine whether or not it was</p> <p>11 complied with, right?</p> <p>12 MR. FOX: Objection to form.</p> <p>13 A. I was able to use the revision</p> <p>14 history to see what changes had been made</p> <p>15 since that time, and as I sit here now, I</p> <p>16 can't explain that in detail because I don't</p> <p>17 have the document in front of me. But I</p> <p>18 concluded I had enough information there to</p> <p>19 establish that they did have a procedure for</p> <p>20 that.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. Is the answer to my question</p> <p>23 yes, that the version that was in effect when</p> <p>24 the change was being evaluated, that would be</p>
<p style="text-align: right;">Page 59</p> <p>1 to determine what would have been there in</p> <p>2 that earlier iteration.</p> <p>3 Q. Did you discuss that at all in</p> <p>4 your report?</p> <p>5 A. No.</p> <p>6 Q. Is this just an issue that you</p> <p>7 became aware of this weekend, as you said?</p> <p>8 A. Oh, just the incorrect citation</p> <p>9 of the number I became aware of, yes.</p> <p>10 Q. The wording of the SMP that</p> <p>11 governed the change control for the</p> <p>12 manufacturing process is an important</p> <p>13 document in this case, correct?</p> <p>14 MR. FOX: Objection to form.</p> <p>15 A. It's an important document,</p> <p>16 yes.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. And the version that would be</p> <p>19 most significant would be the version that</p> <p>20 was in effect in 2011 when the manufacturing</p> <p>21 process change was being evaluated at ZHP,</p> <p>22 correct?</p> <p>23 MR. FOX: Objection to form.</p> <p>24 A. Yes, that would be important.</p>	<p style="text-align: right;">Page 61</p> <p>1 the one that would be most significant</p> <p>2 because that would have been the one in</p> <p>3 effect at the time?</p> <p>4 MR. FOX: Objection to form.</p> <p>5 A. That would have been the one in</p> <p>6 effect at the time, and that would be the one</p> <p>7 that GMP would require them to follow, yes.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. And you testified that you</p> <p>10 believed that version 5 or 6 would be the one</p> <p>11 that was in effect at the time of the change,</p> <p>12 and that's the one that would be most</p> <p>13 significant, that's your understanding?</p> <p>14 MR. FOX: Objection to form.</p> <p>15 A. I can't be positive without</p> <p>16 looking at the version history in the actual</p> <p>17 attachment that's referenced here, but from</p> <p>18 memory, I think it was in that vicinity. It</p> <p>19 was either 5 or 6. I'd have to look again to</p> <p>20 be sure.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. If ZHP failed to comply with</p> <p>23 the SMP 18 version that was in effect when it</p> <p>24 did its change control review, then it</p>

<p>Page 62</p> <p>1 violated GMP, correct?</p> <p>2 MR. FOX: Objection. Form.</p> <p>3 A. That would be a deviation from</p> <p>4 GMP, yes.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. I'm not going to pull them out</p> <p>7 right now, but there were also some ICH</p> <p>8 documents that you referenced in your report</p> <p>9 as well, correct?</p> <p>10 A. Yes.</p> <p>11 Q. For example, ICH Q7A and Q7,</p> <p>12 that's the good manufacturing practice</p> <p>13 guidance for active pharmaceutical</p> <p>14 ingredients, that's an important document in</p> <p>15 this case, right?</p> <p>16 MR. FOX: Objection to form.</p> <p>17 A. The correct nomenclature is Q7.</p> <p>18 They dropped the A off of it a few years ago.</p> <p>19 BY MR. SLATER:</p> <p>20 Q. In the 2001 version it said</p> <p>21 Q7A, and then in 2016 they dropped the A.</p> <p>22 Does that sound right?</p> <p>23 A. Yes.</p> <p>24 Q. So for our discussion today, we</p>	<p>Page 64</p> <p>1 BY MR. SLATER:</p> <p>2 Q. And in your industry, it's</p> <p>3 accepted that a violation -- rephrase.</p> <p>4 And in your industry, it's</p> <p>5 accepted that a failure to comply with Q7</p> <p>6 would amount to a GMP violation, correct?</p> <p>7 MR. FOX: Objection to form.</p> <p>8 A. Not exactly.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. Are there circumstances where</p> <p>11 the failure to comply with Q7 constitutes a</p> <p>12 violation of GMP?</p> <p>13 A. Are there circumstances --</p> <p>14 pardon me. Say again? Are there</p> <p>15 circumstances when it does?</p> <p>16 Q. Yes.</p> <p>17 MR. FOX: Objection to form.</p> <p>18 A. Yes.</p> <p>19 BY MR. SLATER:</p> <p>20 Q. I'm saying in and of itself</p> <p>21 where somebody would say, Well, because you</p> <p>22 didn't comply with this aspect of Q7, that</p> <p>23 constitutes a violation of GMP.</p> <p>24 MR. FOX: Objection to form.</p>
<p>Page 63</p> <p>1 can just call it the Q7?</p> <p>2 A. Yes.</p> <p>3 Q. Was ZHP required to comply with</p> <p>4 Q7 at the time that it was evaluating the</p> <p>5 change in the manufacturing process as a</p> <p>6 matter of GMP?</p> <p>7 MR. FOX: Objection to form.</p> <p>8 A. In the US regulatory hierarchy,</p> <p>9 Q7 stands as nonbinding guidance, not as a</p> <p>10 regulation.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. Well, if it's a nonbinding</p> <p>13 guidance, why does anybody look at it if it</p> <p>14 has no impact on anything that anyone is</p> <p>15 actually going to have to do?</p> <p>16 A. Because there is no binding</p> <p>17 regulation for GMP for API, only a broad</p> <p>18 statutory requirement.</p> <p>19 Q. In terms of how the broad</p> <p>20 statutory requirement to comply with GMP is</p> <p>21 interpreted, Q7 is actually a significant</p> <p>22 source, correct?</p> <p>23 A. Yes.</p> <p>24 MR. FOX: Objection to form.</p>	<p>Page 65</p> <p>1 Incomplete hypothetical.</p> <p>2 A. That involves the application</p> <p>3 of judgment. It is not a linear correlation.</p> <p>4 If you deviate from a guideline, you're</p> <p>5 expected to have a justified reason why what</p> <p>6 you are doing to comply is as good as or</p> <p>7 better than what the guideline prescribes.</p> <p>8 So there may be times you don't</p> <p>9 meet the guideline literally, but what you're</p> <p>10 doing is perfectly adequate.</p> <p>11 BY MR. SLATER:</p> <p>12 Q. I think what you're saying is</p> <p>13 if you're going to deviate from the Q7</p> <p>14 guideline, you need to be able to explain why</p> <p>15 the alternative approach you took was</p> <p>16 acceptable?</p> <p>17 A. That's correct.</p> <p>18 Q. And acceptable would mean that</p> <p>19 it -- well, let me rephrase.</p> <p>20 And acceptable would mean that</p> <p>21 your own process or your own approach</p> <p>22 accomplished the same thing that Q7 sought to</p> <p>23 approach, correct?</p> <p>24 MR. FOX: Objection to form.</p>

Page 66

1 A. Yes.

2 BY MR. SLATER:

3 Q. So, for example, if the issue

4 was a -- the Q7 requirement that a thorough

5 scientifically based risk assessment be

6 performed in order to identify potential

7 genotoxic impurities that may result from a

8 change in manufacturing process, if ZHP

9 failed to actually identify that potential

10 impurity, ZHP would need to show why its

11 approach either -- it would need to show why

12 its approach which deviated from Q7 -- let me

13 rephrase, because I think that I actually

14 answered my own question.

15 MR. FOX: I'm going to object

16 to it anyway, Adam.

17 MR. SLATER: I took it back.

18 You can't object to the take-back.

19 BY MR. SLATER:

20 Q. If ZHP did not apply Q7 to its

21 risk assessment for the manufacturing change

22 to the zinc chloride process, ZHP would need

23 to justify why it took an alternative

24 approach, correct?

Page 67

1 MR. FOX: Objection to form.

2 A. Mr. Slater, your question

3 assumes that that level of detail is in Q7,

4 which it is not. If memory serves,

5 Section 2.22 of Q7, line item 4 is one

6 sentence that simply says that when

7 deviations occur they must be investigated.

8 It doesn't mention genotoxic impurities or

9 anywhere near the level of specificity that

10 was embodied in your question.

11 BY MR. SLATER:

12 Q. Can we agree when ZHP performed

13 its risk assessment in connection with the

14 manufacturing process change to the zinc

15 chloride process that ZHP was required to

16 apply current scientific knowledge?

17 MR. FOX: Objection to form.

18 A. Yes.

19 BY MR. SLATER:

20 Q. You said something earlier

21 about from what you saw there was a process

22 that ZHP had, and that's part of GMP, is that

23 you have to have a process to follow, right?

24 A. Yes.

Page 68

1 Q. GMP also requires that the

2 process be followed thoroughly and correctly,

3 right?

4 MR. FOX: Objection to form.

5 A. Yes.

6 BY MR. SLATER:

7 Q. So going through the motions

8 and saying, Well, we checked the boxes and we

9 technically did a risk assessment, that's not

10 enough; you have to actually actively perform

11 the risk assessment and apply the available

12 scientific knowledge in evaluating that

13 process, right?

14 MR. FOX: Objection to form.

15 A. I don't -- I fail to understand

16 the difference between saying you did a risk

17 assessment and doing a risk assessment, which

18 is what your question implied to me, sir.

19 BY MR. SLATER:

20 Q. Well, what I'm saying is, is it

21 enough to just go through the motions and not

22 apply the scientific knowledge that's

23 available and just check the boxes and then

24 you're okay?

Page 69

1 MR. FOX: Objection to form.

2 A. I fail to understand the thrust

3 of your question. I really don't follow you.

4 BY MR. SLATER:

5 Q. Okay. I understand that you

6 have told us you don't have the scientific

7 expertise to determine whether or not --

8 well, rephrase. Let me ask you this, if I'm

9 right.

10 Am I correct that you have told

11 us in your report you do not have the

12 scientific expertise to evaluate whether or

13 not ZHP adequately took into account the

14 scientific knowledge at the time of the

15 manufacturing process change such that you

16 can't offer an opinion as to whether or not

17 ZHP met or did not meet current good

18 manufacturing practices?

19 MR. FOX: Objection to form.

20 A. I am not a subject matter

21 expert in process chemistry or pharmaceutical

22 chemistry, nor was I when I was at the FDA.

23 The way things were done there

24 and the way I do them in my consulting

<p style="text-align: right;">Page 70</p> <p>1 practice is in a multidisciplinary 2 collaborative sense where I call on the 3 knowledge and expertise of other subject 4 matter experts to assist in areas where I 5 don't feel I have all the knowledge and 6 experience necessary. 7 That's the way these things are 8 worked out both in the agency and in the 9 consulting work that I do. 10 BY MR. SLATER: 11 Q. In response to my question, "am 12 I correct," is the answer yes? 13 MR. FOX: Objection to form. 14 A. I don't -- I am not a subject 15 matter expert in process chemistry or 16 pharmaceutical chemistry, so there are 17 limitations for how far I could take that 18 analysis, yes. 19 BY MR. SLATER: 20 Q. And am I correct that because 21 you do not offer any opinions regarding the 22 scientific adequacy of the risk assessment, 23 you're not offering an opinion at this time 24 as to whether or not ZHP met its GMP</p>	<p style="text-align: right;">Page 72</p> <p>1 form. 2 Sorry, Adam. 3 BY MR. SLATER: 4 Q. -- am I correct that you cannot 5 do so because of your lack of scientific 6 expertise? 7 MR. FOX: Objection to the 8 form. Misstates testimony, no 9 foundation. 10 A. I would require the assistance 11 of scientific subject matter experts to have 12 a fully formed opinion of that, that's 13 correct. 14 BY MR. SLATER: 15 Q. Well, when you say to have a 16 fully formed opinion, I just want to make 17 sure before we get off this point that we're 18 both clear. 19 You don't have an opinion as 20 you sit here right now as to whether ZHP 21 satisfied good manufacturing practices when 22 it made the manufacturing process change 23 because you're not able to evaluate the 24 scientific adequacy of that risk assessment,</p>
<p style="text-align: right;">Page 71</p> <p>1 obligations? 2 MR. FOX: Objection to the 3 form. Misstates testimony. 4 BY MR. SLATER: 5 Q. Am I correct? 6 A. In my report I indicate those 7 areas where I must defer to appropriate -- 8 people with appropriate scientific expertise. 9 Q. And that's one of those areas, 10 right? 11 MR. FOX: Objection to form. 12 A. It may be. As I recall it is, 13 but I'm not looking at that part of the 14 report at the moment. 15 BY MR. SLATER: 16 Q. Well, I'm asking you as you sit 17 here right now, am I correct that because 18 you're not able to offer an opinion as to 19 whether or not ZHP's risk assessment was 20 adequate from a scientific perspective, 21 you're not in a position to offer an opinion 22 as to whether ZHP's risk assessment was 23 adequate from a GMP perspective -- 24 MR. FOX: Objection to the</p>	<p style="text-align: right;">Page 73</p> <p>1 is that correct? 2 MR. FOX: Objection to form. 3 A. I'm not able to determine 4 independently whether it was feasible for 5 them to have brought the scientific 6 principles to bear beyond what they did, 7 because I am not a pharmaceutical chemist or 8 a process scientist, and not aware of what 9 the state of the art may have been at that 10 point in time. That's what I would need help 11 on. I can't evaluate other aspects of the 12 risk assessment. 13 And assuming the science is 14 sound, I can then offer an opinion that if 15 that is true, then the effort complies with 16 GMP. But it's subject to validation by 17 appropriate scientific expertise. 18 BY MR. SLATER: 19 Q. At this point you don't have an 20 opinion as to whether ZHP met or did not meet 21 GMP because you do not at this time have a 22 basis to evaluate the scientific adequacy of 23 the risk assessment. Is that a correct 24 statement?</p>

Page 74	Page 76
<p>1 MR. FOX: Objection to form.</p> <p>2 Misstates testimony and his report.</p> <p>3 A. Assuming the science is</p> <p>4 supportable I can form an opinion, but I</p> <p>5 would need additional input in order to be</p> <p>6 confident.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. I understand what you could do</p> <p>9 if certain information were provided at a</p> <p>10 later date.</p> <p>11 But as you sit here now, you're</p> <p>12 not able to form that opinion because you</p> <p>13 don't have that information one way or the</p> <p>14 other, correct?</p> <p>15 A. That's correct.</p> <p>16 MR. FOX: Objection to form.</p> <p>17 BY MR. SLATER:</p> <p>18 Q. I'm sorry, over the objection</p> <p>19 you said "that's correct," right?</p> <p>20 A. Yes.</p> <p>21 Q. You said that -- I think you</p> <p>22 used words to the effect of -- rephrase.</p> <p>23 When you were talking a few</p> <p>24 moments ago you referred to the feasibility</p>	<p>1 would be able to reach a conclusion I would</p> <p>2 be confident in. It would require study and</p> <p>3 discussion.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. Well, I would like you to</p> <p>6 assume that it was feasible for ZHP to know</p> <p>7 at the time that it was performing its risk</p> <p>8 assessment on the zinc chloride process that</p> <p>9 under those manufacturing conditions DMF</p> <p>10 could degrade and create dimethylamine, and</p> <p>11 that it was also feasible to know that under</p> <p>12 those manufacturing conditions that</p> <p>13 dimethylamine could react with the nitrous</p> <p>14 acid that resulted from the sodium nitrate at</p> <p>15 the quenching stage, and that that reaction</p> <p>16 could form NDMA or other nitrosamines, I'd</p> <p>17 like you to assume that that was feasible for</p> <p>18 them to know at the time, and they did not --</p> <p>19 as we know, they did not identify that</p> <p>20 potential impurity and that potential</p> <p>21 reaction, we know that.</p> <p>22 So if my hypothetical is</p> <p>23 correct, ZHP violated GMP in its risk</p> <p>24 assessment, correct?</p>
Page 75	Page 77
<p>1 of having certain scientific knowledge, or</p> <p>2 something to that effect. I know I'm not</p> <p>3 directly quoting you. But I think you said</p> <p>4 something to that effect.</p> <p>5 Did I hear you right?</p> <p>6 A. Yes.</p> <p>7 MR. FOX: Objection to form.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. If it was feasible for ZHP to</p> <p>10 be aware of the scientific processes that led</p> <p>11 to the creation of the NDMA impurity at the</p> <p>12 time it did its risk assessment, then it</p> <p>13 violated GMP by failing to identify that</p> <p>14 potential impurity, correct?</p> <p>15 MR. FOX: Objection to the</p> <p>16 form. Misstates testimony, no</p> <p>17 foundation.</p> <p>18 A. If it was feasible for them to</p> <p>19 apply appropriate science at that point in</p> <p>20 time and they failed to do so, it would raise</p> <p>21 certain questions and would require further</p> <p>22 study on my part and collaboration with the</p> <p>23 appropriate scientific experts so that I</p> <p>24 could fully understand the details before I</p>	<p>1 MR. SLATER: Objection to form.</p> <p>2 Incomplete hypothetical.</p> <p>3 A. Part of a proper vetting of</p> <p>4 that position would require understanding</p> <p>5 whether analytical methodology existed that</p> <p>6 could detect NDMA at whatever level it might</p> <p>7 or might not be present, and how much</p> <p>8 reliability could be placed in that</p> <p>9 analytical methodology.</p> <p>10 So that's another example of</p> <p>11 the sort of thing I would need the help of</p> <p>12 pharmaceutical chemistry expertise to better</p> <p>13 understand.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. The analytical methodology</p> <p>16 would be GC-MS, gas chromatography-mass</p> <p>17 spectrometry, right?</p> <p>18 MR. FOX: Objection to form.</p> <p>19 A. That's one of, I believe, three</p> <p>20 methods that are out there now that were not</p> <p>21 at the time in question.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. I'd like to expand my</p> <p>24 hypothetical to address the comment you just</p>

<p style="text-align: right;">Page 78</p> <p>1 made, and I'd like you to assume that it was 2 feasible based on technology available in 3 2011 for ZHP to have identified the NDMA if 4 they were looking for it as a potential 5 impurity. I'd like you to assume that 6 technology was available. 7 Having expanded my hypothetical 8 accordingly, you would agree that under those 9 circumstances ZHP would have violated GMP in 10 its risk assessment, correct? 11 MR. FOX: Objection to form. 12 A. Well, you're asking me to make 13 a lot of assumptions, which I do not know 14 whether they're true or not, and I frankly 15 struggle with that. I'm not sure I can agree 16 to that hypothetical. 17 BY MR. SLATER: 18 Q. We'll come back to it. 19 You said you normally work with 20 a multidisciplinary team to form your GMP 21 opinions in this type of a context? 22 A. I said that I did that when I 23 was at the FDA, and that in consulting I 24 still do that to this day.</p>	<p style="text-align: right;">Page 80</p> <p>1 you did in your report, right? 2 A. That's right. 3 MR. FOX: Objection to form. 4 Misstates testimony. 5 A. What I did was I mentioned 6 specifically in the report the areas where I 7 was unable to carry my opinion beyond the 8 point it's at because I would need to defer 9 to others with appropriate scientific 10 expertise. Those areas are highlighted. 11 BY MR. SLATER: 12 Q. I want to come back now to my 13 hypothetical. And it's no secret I'm asking 14 you these questions as a hypothetical because 15 I think I can prove every single aspect of it 16 very easily. So this is not some -- I'm just 17 telling you this is no farfetched 18 hypothetical. So let me -- having said that, 19 let me rephrase. 20 Were you provided the report of 21 Dr. Steven Hecht? 22 A. No. 23 Q. Do you know who he is? 24 A. No.</p>
<p style="text-align: right;">Page 79</p> <p>1 Q. That did not occur here, right? 2 A. It did not, because my 3 retention was under a particular agreement, 4 and I didn't have the benefit of being able 5 to call upon colleagues and share details 6 with them due to confidentiality. 7 Q. You did not rely on the 8 opinions of any subject matter experts 9 regarding the scientific questions here in 10 forming your opinions. That has not 11 occurred, right? 12 MR. FOX: Objection to the 13 form. Misstates his report and 14 references. 15 BY MR. SLATER: 16 Q. I'm correct, right? 17 A. I took what was available from 18 the FDA communications and the record that I 19 had in front of me and based my opinion on 20 that. 21 Q. I didn't see any discussion in 22 your report of you relying on any particular 23 subject matter experts regarding the science 24 to form your opinions. That's not something</p>	<p style="text-align: right;">Page 81</p> <p>1 Q. Were you -- rephrase. 2 Were you provided, other than 3 Mr. Quick's declaration and Ms. Conti's 4 declaration, any other plaintiff expert 5 reports or declarations? 6 A. No. 7 Q. I'm going to try this one more 8 time, but I'm going to try to do it more 9 coherently. 10 Let me ask you this before I go 11 on. Actually let me do this, actually, the 12 way that I want to. 13 All right. I'm going to try to 14 ask you the hypothetical in a little more 15 condensed fashion now also addressing the 16 analytical methodology issue that you 17 questioned me on so I can put it all together 18 in one question, and then we'll see if, maybe 19 by me doing that, if you'll be able to answer 20 that question, okay? 21 A. Sure. 22 Q. I'd like you to assume that at 23 the time -- rephrase. 24 I would like you to assume that</p>

<p style="text-align: right;">Page 82</p> <p>1 at the time ZHP was performing its risk 2 assessment on the zinc chloride manufacturing 3 process that it was scientifically feasible 4 for ZHP to know that, under the manufacturing 5 process conditions that were proposed, that 6 the DMF that they had added to the process 7 could degrade, and that one of the degradings 8 from that could be dimethylamine, and that 9 under the proposed manufacturing conditions 10 that dimethylamine could react with the 11 nitrous acid that would be present during the 12 quenching phase due to the presence of sodium 13 nitrate, and that that reaction could yield 14 NDMA.</p> <p>15 I'd like you also to assume 16 that at the time it would have been 17 scientifically feasible to apply testing to 18 see if there was NDMA there if one were 19 looking for it. I'd like you to assume those 20 facts.</p> <p>21 If those facts are true, you 22 would agree with me that ZHP's failure to 23 take into consideration what I just asked you 24 about would have violated current good</p> <p style="text-align: right;">Page 83</p>	<p style="text-align: right;">Page 84</p> <p>1 conclusion by reviewing the information they 2 submitted.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. If ZHP did not take into 5 account the chemical reactions that I just 6 described to you in my hypothetical, then 7 they violated good manufacturing practices, 8 correct?</p> <p>9 MR. FOX: Objection to the 10 form. Misstates testimony, calls for 11 speculation.</p> <p>12 A. What I -- I'm sorry? I heard 13 an echo there, I guess. I thought someone 14 was asking another question.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. No, no one said anything. But 17 let me just be clear on my question before 18 you answer.</p> <p>19 I'm going back to my original 20 question, which is, assuming the accuracy of 21 that hypothetical, assuming that it was 22 scientifically feasible for ZHP to know those 23 things, and assuming they did not take them 24 into account, they violated good</p> <p style="text-align: right;">Page 85</p>
<p>1 manufacturing practices at the time?</p> <p>2 MR. FOX: Objection to the 3 form. Incomplete hypothetical, calls 4 for speculation.</p> <p>5 A. If I understand your question 6 correctly, Mr. Slater, if all those things 7 were feasible and were known to ZHP, they 8 should have taken them into consideration.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. We know they did not, because 11 you've seen their documentation, so we know 12 ZHP never took into account the potential 13 chemical reactions I went through with you, 14 correct?</p> <p>15 MR. FOX: Objection to form.</p> <p>16 A. I can't reach that conclusion. 17 ZHP submitted a tremendous amount of very 18 detailed scientific analysis, a lot of 19 structural chemistry diagrams and other 20 things, and this is where my expertise drops 21 off, and I would need others to look at that 22 and determine whether they, in fact, 23 understood the principles you've just 24 outlined or not. I cannot reach that</p> <p style="text-align: right;">Page 85</p>	<p>1 manufacturing practices in that risk 2 assessment, correct?</p> <p>3 MR. FOX: Objection to form. 4 No foundation, misstates testimony, 5 and calls for speculation.</p> <p>6 A. The GMP requirement is very 7 high level, it's for a thorough 8 investigation. Nowhere does it specify what 9 the elements of a thorough investigation are; 10 it leaves that up to judgment.</p> <p>11 And certainly if there is 12 material information that was either not 13 considered, omitted, whatever, then that risk 14 assessment would be less than it should be 15 based upon those facts.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. When you say "less than it 18 should be," that would mean not compliant 19 with GMP, correct?</p> <p>20 MR. FOX: Objection to form.</p> <p>21 A. That calls for a conclusion 22 that I'm not prepared to reach. It would be 23 less than I would hope to see certainly. 24 But it's difficult sometimes to</p>

Page 86

1 discern when you're talking about something
2 would simply improve an otherwise compliant
3 practice or make the difference between
4 compliance and noncompliance.
5 BY MR. SLATER:
6 Q. Are you aware that there was --
7 well, let's jump forward a little bit,
8 actually, since we're cruising along here.
9 Just find a paperclip. We'll come back to
10 this a little bit.
11 Let me ask you this: On your
12 Exhibit B, did you actually review the change
13 request form which laid out the evaluation
14 that ZHP did of its change in manufacturing
15 process to the zinc chloride process?
16 Because I didn't see that referenced on your
17 reliance list -- reference list, I should
18 say.
19 A. I think it was incorporated in
20 another document that is on that list, but it
21 would take me some time to check back and
22 find it. I do recall seeing that form, but I
23 don't remember much about it as I sit here.
24 Q. I didn't see the change request

Page 87

1 form referenced anywhere in your report. Did
2 I miss that, or am I correct that it's not
3 referenced?
4 MR. FOX: Objection. Asked and
5 answered.
6 A. It may not have been referenced
7 by that name. I think it was a part of
8 another document set that I reviewed and
9 relied upon. And if memory serves, I believe
10 it was the response to the warning letter,
11 but I would have to go back and check through
12 these references to determine that for
13 certain.
14 BY MR. SLATER:
15 Q. The documentation of the risk
16 assessment for the change in manufacturing
17 process, that documentation would have been
18 very important to you in forming your opinion
19 here, correct?
20 MR. FOX: Objection to form.
21 A. Yes.
22 BY MR. SLATER:
23 Q. Yet there's no place in your
24 report where you actually discuss that

Page 88

1 document at all, correct?
2 A. What do you mean by "that
3 document"? Which document are you referring
4 to?
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 anywhere in your report or discussed at all
10 in your report. Am I correct?
11 A. I don't recall specifically
12 citing it. I do recall seeing it.
13 Q. The change request form
14 documenting what was done and what was
15 considered would be a critical document to
16 you in forming an opinion as to whether or
17 not ZHP met its GMP obligations, right?
18 MR. FOX: Objection to form.
19 Argumentative, and misstates prior
20 testimony. Asked and answered.
21 A. Subject to input regarding the
22 rigor of the science, yes.
23 MR. SLATER: Counsel, you keep
24 saying that I'm misstating testimony.

Page 89

1 I don't understand why you keep saying
2 that. I'm not stating his testimony.
3 I mean, I think we have to at
4 some point -- I would ask you politely
5 if we can just limit the objections to
6 legitimate objections, please.
7 MR. FOX: It was a legitimate
8 objection, Adam. You previously asked
9 him whether it was important, now
10 you're asking him whether it's
11 critical. You were changing the
12 question on him, and you had already
13 asked about that.
14 BY MR. SLATER:
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 [REDACTED]

Page 90

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]
14 [REDACTED]
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 [REDACTED]

Page 91

1 Q. As a matter of ICH guidance, if
2 something is deemed a critical change, it
3 requires a higher degree of scientific rigor
4 in performing the risk assessment, right?
5 MR. FOX: Objection to form.
6 A. Generally speaking, yes.
7 BY MR. SLATER:
8 Q. Do you know whether or not --
9 well, rephrase.
10 You said you think that you saw
11 the change request form as an attachment to
12 another document. Did you ever ask counsel,
13 Is this the complete change request form with
14 all attachments?
15 A. I don't recall ever asking that
16 question, no.
17 Q. Do you have any knowledge as to
18 whether or not the change request form that
19 you think you saw attached to another
20 document was the complete change request form
21 with all attachments? As you sit here now,
22 do you have any idea?
23 A. I do not as I sit here now.
24 Q. And without seeing the complete

Page 92

1 document and comparing it to what you did
2 have, you don't know whether there's material
3 information that you didn't have available to
4 you, right, by definition?
5 A. I'm not sure I understand your
6 question, sir.
7 Q. Well, you don't know what you
8 don't know, and since you don't know if you
9 saw the complete document you don't know if
10 you were missing material information from
11 the change request form and its attachments,
12 right?
13 MR. FOX: Objection to form.
14 A. If there was material
15 information that was not made available to
16 me, I'm not aware of that, and yes, it would
17 be of concern.
18 BY MR. SLATER:
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 A. I don't recall.
24 Q. Would that be an important

Page 93

1 consideration in forming an opinion as to
2 whether ZHP complied with GMP?
3 MR. FOX: Objection to form.
4 A. That's another example of
5 something that I would ask for help from a
6 pharmaceutical chemistry expert to evaluate,
7 but yes, the outcome of that discussion would
8 be important.
9 BY MR. SLATER:
10 Q. Were you curious when you were
11 writing your report as to what impurities ZHP
12 considered -- let me rephrase.
13 When you were writing your
14 report, were you curious as to what potential
15 impurities ZHP considered as part of its risk
16 assessment for the zinc chloride process?
17 Were you curious as to what they looked at?
18 A. I'm not sure I understand what
19 you mean by was I curious. I reviewed the
20 record, I saw what they did consider, I saw
21 how they documented it, I stated, I think
22 fairly clearly, where my limitations were in
23 my ability to evaluate the science.
24 Was I curious as to whether

Page 94

1 they looked for certain other things that
2 they might have had no reason to believe were
3 there? No. GMP does not require that you
4 look for things you have no basis to believe
5 are present.
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 BY MR. SLATER:
14 Q. As you sit here now, did you
15 say anything about that in your report?
16 A. Again, I'd have to go through
17 the report to be certain.
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 Are you saying it might be in the report and
22 you'd need to check your report to see if
23 that's in there?
24 A. I don't recall that it's there,

Page 95

1 but I wouldn't be prepared to say that
2 definitively without going through the
3 report.
4 Q. And as you sit here now, are
5 you able to tell me one way or another
6 whether or not -- well, let me ask you this.
7 As you sit here now, do you
8 have an assumption as to whether or not ZHP
9 considered the potential formation of NDMA or
10 any other nitrosamines as part of the zinc
11 chloride manufacturing process when it
12 performed its risk assessment? Do you have
13 an assumption one way or the other as to
14 whether that was considered?
15 A. My assumption would be that
16 they did, absent information to the contrary.
17 But I don't recall what those documents said
18 without going back and looking at them again.
19 This was an incredibly voluminous data set,
20 and I don't carry it all around in my head.
21 Q. What's the basis for that
22 assumption that they did consider the
23 potential formation of NDMA or other
24 nitrosamines as part of the risk assessment?

Page 96

1 A. It's the impression I got of
2 the thoroughness and completeness of the
3 documents that I reviewed from ZHP, the
4 interactions between them and the FDA staff,
5 the FDA questions that came back to them, the
6 entire dialogue that took place there.
7 Ultimately they did, of course,
8 find those residues in certain batches, and
9 they did the responsible thing and conducted
10 a recall, so at some point in time they did
11 make that identification. I believe that was
12 in 2018.
13 Q. When you say "they did the
14 responsible thing," do you mean telling their
15 customers and the FDA that there was NDMA in
16 the valsartan?
17 A. Once they knew that, yes.
18 Q. When you say that's the
19 responsible thing, it's not only the
20 responsible thing, it was the legally
21 required thing to do, right?
22 A. Yes.
23 MR. FOX: Objection to form.
24 ///

Page 97

1 BY MR. SLATER:
2 Q. As soon as ZHP knew that there
3 was NDMA in its valsartan, it was legally
4 obligated to inform all of its customers and
5 the FDA, correct?
6 MR. FOX: Objection to form.
7 Calls for a legal conclusion.
8 A. The regulatory requirement is
9 for them to report that to the FDA in the
10 form of a report called a field alert report.
11 BY MR. SLATER:
12 Q. And it's your testimony based
13 on the materials you saw that you understand
14 that ZHP complied with that field alert
15 report regulation in June of 2018?
16 A. They notified the FDA.
17 Q. It's your understanding that
18 ZHP notified its customers and the FDA
19 immediately upon learning that there was NDMA
20 in its valsartan? Is that your understanding
21 from what you reviewed?
22 MR. FOX: Objection to form.
23 A. The word "immediately" is one I
24 have difficulty with. They did it very soon

<p>Page 98</p> <p>1 thereafter. I don't know what you mean by</p> <p>2 "immediate," but it was in very close</p> <p>3 proximity time-wise to that, yes.</p> <p>4 BY MR. SLATER:</p> <p>5 Q. The field alert report</p> <p>6 regulation provides three business days to</p> <p>7 provide that information to the FDA, right?</p> <p>8 A. Yes.</p> <p>9 Q. Is it your understanding that</p> <p>10 ZHP reported that there was NDMA in its</p> <p>11 valsartan within three days -- business days</p> <p>12 of learning of that?</p> <p>13 MR. FOX: Objection to form.</p> <p>14 A. The difficulty with that is</p> <p>15 it's very difficult to determine in many</p> <p>16 cases when the clock starts.</p> <p>17 I believe they did the</p> <p>18 responsible thing by reporting it. Once they</p> <p>19 had certainty as to that information they</p> <p>20 told the FDA about it, and they did conduct a</p> <p>21 recall on a voluntary basis.</p> <p>22 BY MR. SLATER:</p> <p>23 Q. Was the notification of the</p> <p>24 presence of NDMA in the valsartan to</p>	<p>Page 100</p> <p>1 chloride process during its risk assessment.</p> <p>2 You told me that you assumed they took that</p> <p>3 into account, right?</p> <p>4 A. It would appear that they did</p> <p>5 from the depth of the scientific information</p> <p>6 they submitted. But again, that's one of</p> <p>7 those areas where I would turn to the subject</p> <p>8 matter expertise -- or a person with</p> <p>9 appropriate subject matter expertise to help</p> <p>10 me understand how far they carried things and</p> <p>11 whether that was sufficient to achieve those</p> <p>12 ends. I didn't --</p> <p>13 Q. Go ahead, I'm sorry.</p> <p>14 A. I was going to say I made no</p> <p>15 attempt to evaluate the science</p> <p>16 independently.</p> <p>17 Q. Whether or not ZHP considered</p> <p>18 the potential formation of nitrosamines as</p> <p>19 part of the zinc chloride process is an</p> <p>20 important fact you would want to know, right?</p> <p>21 MR. FOX: Objection to form.</p> <p>22 A. Along with whether or not it</p> <p>23 was even reasonable for them to consider that</p> <p>24 at that point in time. I think that's the</p>
<p>Page 99</p> <p>1 customers and the FDA required by good</p> <p>2 manufacturing practices?</p> <p>3 A. No.</p> <p>4 MR. FOX: Objection to form.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Did good manufacturing</p> <p>7 practices require that -- well, rephrase.</p> <p>8 I'll get back to it.</p> <p>9 Coming back to what ZHP did as</p> <p>10 part of its risk assessment -- well,</p> <p>11 rephrase.</p> <p>12 I was asking you before about</p> <p>13 whether ZHP considered the potential</p> <p>14 formation of nitrosamine impurities including</p> <p>15 NDMA, and you said your assumption was that</p> <p>16 they did consider that, right?</p> <p>17 MR. FOX: Can you repeat that,</p> <p>18 Adam? I missed that.</p> <p>19 MR. SLATER: Sure.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. You told me a moment ago that</p> <p>22 you assumed that ZHP did as part of its risk</p> <p>23 assessment take into account the potential</p> <p>24 formation of nitrosamines as part of the zinc</p>	<p>Page 101</p> <p>1 other aspect of this. There's nothing in GMP</p> <p>2 that requires you to look for things you</p> <p>3 would have no basis to believe were there.</p> <p>4 And that's why the state of the art of the</p> <p>5 science at that moment in time is important</p> <p>6 for me to understand in tandem with the other</p> <p>7 information.</p> <p>8 BY MR. SLATER:</p> <p>9 Q. Well, my first question is</p> <p>10 this. One important fact for you to consider</p> <p>11 in this matter would be whether or not ZHP</p> <p>12 considered the potential formation of</p> <p>13 nitrosamine impurities as part of the</p> <p>14 proposed zinc chloride process when it</p> <p>15 performed its risk assessment.</p> <p>16 Would you agree with that</p> <p>17 statement?</p> <p>18 A. It would be helpful to</p> <p>19 understand that, yes.</p> <p>20 Q. Did you ask the lawyers who</p> <p>21 retained you if there's any information</p> <p>22 available to answer that question one way or</p> <p>23 another?</p> <p>24 A. I don't recall asking that</p>

Page 102

1 question.
2 Q. That's my question. I want to
3 know if you asked them for that. Okay.
4 A. No.
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]
14 [REDACTED]
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 [REDACTED]

Page 103

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]
14 [REDACTED]
15 MR. FOX: Is this a good time
16 for a break, Adam?
17 MR. SLATER: I need a couple
18 more minutes. I'd like to continue.
19 I don't want to just arbitrarily take
20 a break now.
21 BY MR. SLATER:
22 Q. If there was deposition
23 testimony from corporate representatives of
24 ZHP that definitively answered that question,

Page 104

1 would you like to have been provided that
2 deposition testimony?
3 A. Yes.
4 Q. If such testimony exists one
5 way or another, you would actually expect
6 that that would have been provided to you so
7 that you could perform your function here,
8 right?
9 A. It would have been helpful.
10 Q. Can you think of any legitimate
11 reason why the lawyers who hired you would
12 not have provided you that deposition
13 testimony if, in fact, it exists?
14 MR. FOX: Objection.
15 Argumentative.
16 A. I don't know what the basis was
17 for the document set that I was provided. I
18 can't speculate about what might have been in
19 their minds as to what I would need or what I
20 wouldn't.
21 BY MR. SLATER:
22 Q. If there was a feasible
23 scientific basis for ZHP to know that
24 nitrosamines could potentially be formed by

Page 105

1 the zinc chloride manufacturing process that
2 was being proposed, if that was feasible to
3 know, and if the technology existed for ZHP
4 to feasibly test to see if a nitrosamine was
5 being created by this new manufacturing
6 process, then ZHP would have been required to
7 carry out such testing to see if nitrosamines
8 were being created as part of its risk
9 assessment, correct?
10 MR. FOX: Objection to form.
11 A. That would have been the right
12 thing for them to do. The requirements don't
13 speak to that level of detail, but that would
14 have been a reasonable thing for them to do,
15 yes.
16 BY MR. SLATER:
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 [REDACTED]

Page 106

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 BY MR. SLATER:
7 Q. But you, as somebody who holds
8 himself out as an expert on GMP, would look
9 at what the company actually put in force in
10 its own internal SOPs to address its own
11 business, and based on what you've seen you
12 would agree GMP as applied by ZHP would have
13 required that to be done, right?
14 MR. FOX: Objection to form.
15 A. If their procedure called for
16 identification or quantitation of known
17 potential impurity risk and they failed to do
18 so, then yes, that would be a failure to
19 follow their own procedure, which by
20 extension is a failure to follow GMP.
21 BY MR. SLATER:
22 Q. And you would certainly expect
23 that ZHP or any similar manufacturer would
24 have an internal SOP that would require it to

Page 107

1 identify new impurity risks if they were
2 going to change a manufacturing process,
3 right?
4 A. That's something they should be
5 considering, yes.
6 Q. That would be required by GMP
7 under those circumstances, right?
8 MR. FOX: Objection to form.
9 A. Broadly, yes, but not
10 specifically.
11 BY MR. SLATER:
12 Q. Well, if you were brought in by
13 ZHP or a similar company and asked, We're
14 changing our manufacturing process for this
15 API, would GMP require that that evaluation
16 that we're going to perform evaluate whether
17 any new impurities are being formed, you
18 would say yes, right?
19 A. Yes.
20 Q. If you want to take a break --
21 I'm happy to keep going, Mr. Chesney, your
22 counsel asked if we need a break, I don't
23 need one. I'm happy to keep going because
24 I'm hoping to get done in the afternoon, but

Page 108

1 it's completely up to you. If you want to
2 keep going, I'll keep going.
3 MR. FOX: We've been --
4 THE WITNESS: Go ahead, Tom.
5 MR. FOX: What did you say,
6 David?
7 THE WITNESS: I was just going
8 to say I could use about ten minutes
9 at this point.
10 MR. SLATER: All right. Let's
11 take ten minutes.
12 THE VIDEOGRAPHER: The time is
13 11:25 a.m. We are off the record.
14 (Whereupon, a recess was
15 taken.)
16 THE VIDEOGRAPHER: The time is
17 11:36 a.m. We are back on the record.
18 BY MR. SLATER:
19 Q. I want to talk a little bit
20 about the significance of the risk assessment
21 for a couple minutes with you.
22 The risk assessment
23 performed -- rephrase.
24 The risk assessment that was

Page 109

1 required to be performed by ZHP has
2 significance for process validation in the
3 sense that you have to identify potential
4 impurities so that you know to test for them.
5 Is that a true statement?
6 A. Generally speaking, yes.
7 Q. So identification of the
8 potential impurities from a new manufacturing
9 process is really a very important threshold
10 step pursuant to GMP, correct?
11 MR. FOX: Objection to form.
12 A. To the extent that it's
13 feasible to do so and you know what to
14 expect, yes.
15 BY MR. SLATER:
16 Q. When you say you know what to
17 expect, meaning you know that this is a
18 potential impurity so you know that you need
19 to test for it?
20 A. Yes. You don't need to conjure
21 up things that there's no rational basis to
22 believe what happened.
23 Q. And this risk assessment is not
24 supposed to be based on guesswork, it's

<p style="text-align: right;">Page 110</p> <p>1 supposed to be based on scientific analysis, 2 right? 3 A. Yes. 4 MR. FOX: Objection to form. 5 BY MR. SLATER: 6 Q. For example, in a situation 7 like this, a company like ZHP would be 8 expected by GMP to have process chemists 9 evaluating the proposed chemical reactions, 10 and to bring their scientific knowledge to 11 bear to identify the potential impurities 12 that could result, right? 13 A. Yes. 14 Q. And they would -- rephrase. 15 And these process chemists 16 would be expected to not only bring to bear 17 their own knowledge that's in their mind, but 18 also to, to the extent they don't know the 19 answer, to research available medical 20 literature, right? 21 Let me rephrase because I went 22 all over the place. I meant to say 23 scientific. 24 And those process chemists</p>	<p style="text-align: right;">Page 112</p> <p>1 identified during the risk assessment is so 2 that not only the process validation can be 3 thorough, but also so that ultimately the 4 specifications for what needs to be tested 5 and what the levels that should be tested for 6 so that those can be set as well, right? 7 A. Yes. 8 Q. And I guess the specifications 9 is sort of the other side of the coin from 10 the process validation. Is that a fair 11 assumption? The process validation is 12 when -- it actually doesn't make sense. You 13 don't have to answer that. You roll your 14 eyes, I know I move on. 15 If there was a GMP violation in 16 the risk assessment, as I have proposed to 17 you through my hypothetical, and ultimately 18 ZHP should have but failed to evaluate the 19 potential nitrosamine impurities that could 20 have resulted from the zinc chloride process, 21 if that's so, and then they went ahead and 22 used that manufacturing process, that process 23 would not be cGMP compliant based on the GMP 24 violation in the risk assessment, correct?</p>
<p style="text-align: right;">Page 111</p> <p>1 would be expected to not only employ their 2 own personal knowledge, but also to research 3 scientific literature as well to the extent 4 that it existed, right? 5 MR. FOX: Objection to form. 6 A. Any literature reports they're 7 aware of, they should be taken into 8 consideration if they're relevant. 9 BY MR. SLATER: 10 Q. And this should be an active 11 process of research and evaluation, right? 12 They should be actively looking to make sure 13 that they turn over the stones that can be 14 turned so they don't miss something, right? 15 MR. FOX: Objection to form. 16 A. Well, yes. Within reasonable 17 limits. You don't have to stay in search 18 mode forever. There comes a point in time 19 when you've consulted appropriate reference 20 materials and feel that you have enough to go 21 on. That's a matter of judgment. 22 BY MR. SLATER: 23 Q. One of the other important 24 reasons why potential impurities need to be</p>	<p style="text-align: right;">Page 113</p> <p>1 MR. FOX: Objection to form. 2 A. That would require me to accept 3 a lot of the assumptions that you're building 4 into your hypothesis. 5 BY MR. SLATER: 6 Q. I'm asking you to accept those 7 assumptions. 8 If those assumptions are -- if 9 the answer is yes, if you accept them, am I 10 correct that the manufacturing process itself 11 would not be GMP compliant? 12 MR. FOX: Objection to form. 13 Incomplete hypothetical. 14 A. Well, that's not the way I 15 would put it, Mr. Slater, that the GMP -- or 16 that the manufacturing process would not be 17 GMP compliant. I would simply say there was 18 material information about the risks inherent 19 in that process that had not been identified. 20 The point in time when this 21 took place, if I remember correctly, was 22 2011, 2012, something like that. Again, 23 without referring to the references, I can't 24 be sure. But I think the FDA in their public</p>

Page 114

1 statements later on indicated the general
 2 awareness of these risks wasn't really known
 3 in the industry or even to the regulators
 4 until much later. So that's why I'm a little
 5 concerned about the validity of some of these
 6 assumptions.
 7 BY MR. SLATER:
 8 Q. And I'm going to go through
 9 that with you a little more. But let me ask
 10 you this. I want to go back to what I was
 11 asking.
 12 If you make the assumptions
 13 that I've asked you to make as to the
 14 inadequacy of the risk assessment, and if you
 15 make those assumptions, which you can assume
 16 those things are hypothetical as an expert as
 17 you know, and the risk assessment violated
 18 GMP, would it also be a violation of GMP to
 19 then manufacture with that manufacturing
 20 process which is creating NDMA?
 21 MR. FOX: Objection to form.
 22 A. Well, if we can be clear that
 23 I'm not accepting the assumptions, just
 24 viewing them purely as hypotheticals, then my

Page 115

1 answer would be yes. But I'm really not
 2 clear that the underlying assumptions are
 3 accurate at this point.
 4 BY MR. SLATER:
 5 Q. At the time ZHP developed the
 6 zinc chloride process, to your knowledge was
 7 any other API manufacturer for valsartan, or
 8 any other sartan for that matter, using the
 9 zinc chloride process in the world?
 10 A. I don't know.
 11 Q. Are you aware of whether or not
 12 there was any potential risk of the creation
 13 of nitrosamines with the original
 14 manufacturing process for valsartan, for the
 15 branded form of the drug, did you ever look
 16 to see whether or not that manufacturing
 17 process had a similar risk?
 18 A. I did not because that would
 19 get into process chemistry, which is outside
 20 my area of expertise.
 21 Q. Give me one second.
 22 Sorry, I'm just digging through
 23 a pile because my goal in life is to not make
 24 the deposition last longer than necessary.

Page 116

1 Okay.
 2 A. That's appreciated, sir.
 3 Q. There's no reason to go longer
 4 than necessary.
 5 MR. SLATER: Okay. Let's go,
 6 Chris, if you can do this, I want to
 7 go to what I think was marked
 8 Exhibit 209 previously, the IARC
 9 monograph from May of 1978.
 10 (Whereupon, Chesney Exhibit
 11 Number 5 was marked for
 12 identification.)
 13 BY MR. SLATER:
 14 Q. It's probably going to take a
 15 moment because I just pulled something out of
 16 order. Look at that.
 17 Okay. Mr. Chesney, have you
 18 ever seen -- and Chris could scroll up for
 19 you to show you what this is.
 20 MR. SLATER: Maybe you could
 21 scroll up a little bit, show the
 22 bottom half also, or maybe make it fit
 23 the screen a little better. There we
 24 go.

Page 117

1 Q. And we can blow it up as you
 2 need, Mr. Chesney, whatever you need.
 3 My first question is, have you
 4 seen this document, the IARC Monographs on
 5 the Evaluation of the Carcinogenic Risk of
 6 Chemicals to Humans, Some N-Nitroso
 7 Compounds, Volume 17, dated in May of 1978?
 8 That's the date in the bottom left. Is this
 9 something you've seen?
 10 A. No.
 11 Q. And you can see it's marked
 12 with an exhibit sticker, Peng Dong ZHP 209.
 13 Do you know who Peng Dong is?
 14 A. The name is vaguely familiar,
 15 but I don't recall.
 16 Q. Okay. I assume you're familiar
 17 with IARC?
 18 A. I've heard of them. I'm not
 19 terribly familiar with them.
 20 Q. The International Agency for
 21 Research on Cancer. That doesn't -- you're
 22 just generally familiar that they exist?
 23 A. That's about it. I haven't had
 24 much to do with that agency over the years.

<p style="text-align: right;">Page 118</p> <p>1 Q. You see that this is a 2 component of -- at the top you can see the 3 "World Health Organization." I assume you've 4 heard of the World Health Organization? 5 A. Oh, of course, yes. 6 Q. And what I'm going to do, if we 7 could, is go to page 36. 8 MR. SLATER: And let's blow up 9 the third full paragraph. Good job. 10 Thank you. Maybe a little smaller. 11 Perfect. 12 Q. Can you see that okay, 13 Mr. Chesney? 14 A. Yes, sir, that's fine. 15 Q. Okay. We're looking here on 16 page 36 of this IARC monograph, the third 17 full paragraph, it says, "It has been known 18 since 1865 that the reaction of dimethylamine 19 hydrochloride with sodium nitrate at an 20 acidic pH yields N-nitrosodimethylamine," 21 which is NDMA. 22 Do you see that? 23 A. Yes. 24 Q. Is this the type of feasible</p>	<p style="text-align: right;">Page 120</p> <p>1 few minutes. 2 As far as what I just showed 3 you, this shows that IARC, an arm of the 4 World Health Organization, published as of 5 1978 that it's been known since 1865 that the 6 reaction that ultimately created the NDMA has 7 been known to scientists. That's what this 8 shows, right? 9 MR. FOX: Objection to form. 10 Calls for speculation. 11 A. That's what the sentence says. 12 MR. SLATER: Okay. Let's go 13 now, if we could, to page 40. And 14 we'll blow up that last paragraph. 15 Perfect. 16 BY MR. SLATER: 17 Q. This says in part, "Most of the 18 chemical and physical properties of the 19 nitrosamines described in these monographs 20 were taken from Druckrey et al," and cites to 21 a 1967 publication. Then it says, and this 22 is the part I wanted to really focus on with 23 you, "The principal techniques employed for 24 the analysis of volatile N-nitrosamines have</p>
<p style="text-align: right;">Page 119</p> <p>1 scientific information you're talking about 2 in terms of the ability of ZHP to have known 3 that this reaction between the DMA that would 4 be a degradant product of the DMF could react 5 with the nitrous acid from the sodium nitrate 6 and form NDMA? Is this the type of feasible 7 scientific information you're talking about? 8 MR. FOX: Objection to the 9 form. Beyond the scope of his report 10 and the scope of his expertise, as 11 he's testified to. 12 A. It's the sort of thing I would 13 expect scientific experts with whom I would 14 collaborate to take into consideration. By 15 itself it is what it is, but it doesn't -- it 16 doesn't go beyond what it says on its face. 17 This tendency was identified a long time ago. 18 But it says nothing with 19 respect to the process itself. I'd have to 20 have somebody make that connection for me. 21 BY MR. SLATER: 22 Q. I understand. And I have a few 23 different pieces to the puzzle that I'm 24 planning to probably show you over the next</p>	<p style="text-align: right;">Page 121</p> <p>1 been described in a recent publication 2 (Preussmann et al, 1978). The relative 3 merits of high- and low-resolution mass 4 spectrometry are discussed, since use of mass 5 spectrometry as a confirmatory technique is 6 particularly important." 7 Do you see what I just read? 8 A. Yes. 9 Q. So again, this is addressing 10 the issue of whether or not analytical 11 methods were available to actually detect the 12 NDMA in 2011, 2012, and this is showing that 13 as of 1978, it was being discussed in the 14 World Health Organization publication that 15 mass spectrometry was one available method. 16 Do you see that? 17 MR. FOX: Objection to the 18 form, and incomplete recitation of the 19 document. 20 BY MR. SLATER: 21 Q. Okay. You see that, right, 22 Mr. Chesney? 23 A. I do. 24 Q. Okay. And again, this is the</p>

Page 122

1 type of feasibly available scientific
2 information that you were talking about
3 earlier that you would expect ZHP's
4 scientists to be aware of when they were
5 doing their risk assessment, right?
6 MR. FOX: Objection to form.
7 A. It could constitute an
8 informative data point, but it's by no means
9 the entire picture.
10 MR. SLATER: Okay. Take that
11 document down. Let's go now, Chris,
12 if we could, to Exhibit 311, which is
13 the publication Purification of
14 Laboratory Chemicals.
15 Let me see if this has page
16 numbers.
17 (Whereupon, Chesney Exhibit
18 Number 6 was marked for
19 identification.)
20 BY MR. SLATER:
21 Q. Okay. I've put on the screen a
22 document titled Purification of Laboratory
23 Chemicals, and you can see that it was marked
24 as Exhibit 311 during the deposition of Min

Page 123

1 Li.
2 Do you see that on the screen?
3 A. I do.
4 Q. Do you know who Min Li is?
5 A. The name is familiar from ZHP
6 documents, but I couldn't tell you what
7 position she has, so that she --
8 Q. Or he?
9 A. -- as the case may be, occupies
10 in the company.
11 Q. Okay. And just to be clear,
12 you weren't provided the depositions of Peng
13 Dong or Min Li as part of the materials you
14 were provided, right?
15 A. I don't recall either of those,
16 sir, no.
17 Q. Okay. And, for example, the
18 IARC monograph I just showed you, that's not
19 something you were provided, correct?
20 A. I was not.
21 Q. And this publication, the
22 Purification of Laboratory Chemicals, which
23 was used as a deposition exhibit with Min Li,
24 that's not something you were provided

Page 124

1 either, correct?
2 A. I have not seen this document.
3 MR. SLATER: Chris, let's go to
4 page 192 of this -- actually, stop
5 don't go there yet. Let's go to the
6 second page which has the publication
7 dates. I just want to establish that.
8 Q. We can see that this has a
9 first publication date of 1996 and reprinted
10 in 1998, '99, and 2000.
11 Do you see that?
12 A. I do.
13 MR. SLATER: Let's go now to
14 page 192. Perfect. There you go.
15 You've got it, Chris. If you can blow
16 up that bottom paragraph, and just
17 read the first beginning. Just a tiny
18 bit less because we're cutting off --
19 my picture cuts off. All right.
20 Perfect. Thank you.
21 Q. You see that this references
22 N-N-dimethylformamide, which is DMF.
23 Do you see that?
24 A. Yes.

Page 125

1 Q. And you understand that one of
2 the changes to the manufacturing process when
3 the zinc chloride process was created was to
4 begin to utilize DMF. You're aware of that,
5 right?
6 A. Yes.
7 Q. And this scientific
8 publication, which we know was originally
9 published in 1996 and reprinted up
10 through 2000 on this copy that I am showing
11 you, states that DMF "decomposes slightly at
12 its normal boiling point to give small
13 amounts of dimethylamine and carbon
14 monoxide."
15 Do you see that?
16 A. Yes.
17 Q. And again, this would be the
18 type of feasibly available scientific
19 information you would expect the people at
20 ZHP to have been aware of when they were
21 performing the risk assessment with regard to
22 their decision to add DMF to the
23 manufacturing process, correct?
24 MR. FOX: Objection to form.

Page 126	Page 128
<p>1 A. It would be another data point 2 that would have to be evaluated for its 3 significance and context and understood 4 fully, yes. 5 BY MR. SLATER: 6 Q. The fact that it was known in 7 the scientific community that DMF could 8 decompose to give off small amounts of 9 dimethylamine is certainly something you 10 would have expected the people at ZHP to be 11 aware of when they were formulating and then 12 performing a risk assessment on the zinc 13 chloride process. You could agree with that, 14 correct? 15 MR. FOX: Objection to form. 16 Beyond the scope. 17 A. I would have no ability to form 18 an independent expectation of that. That's 19 the kind of thing I would ask the scientific 20 expert, Is this something they ought to have 21 known about, is this peer-reviewed research, 22 was it -- did it have credibility, was it 23 widely circulated. Those are all things that 24 I would want to take into account to decide</p>	<p>1 definitely Exhibit 197 marked during 2 Min Li's deposition. 3 MR. GEDDIS: 197. Found it. 4 (Whereupon, Chesney Exhibit 5 Number 7 was marked for 6 identification.) 7 BY MR. SLATER: 8 Q. On the screen we have an 9 exhibit that was marked Exhibit 197 actually 10 in the deposition of Peng Dong originally, I 11 can tell you we also showed it to Min Li, and 12 it's published in the medical journal 13 Tetrahedron, or scientific journal I should 14 say, and the title of this article is 15 "N-N-Dimethylformamide: much more than a 16 solvent? 17 Do you see that? 18 A. Yes. 19 Q. And this is dated in 2009. You 20 can see it at the very top. Even though it's 21 very small letters, it says "Tetrahedron," 22 and the year is 2009. 23 A. Yes, I can see it. 24 Q. Great.</p>
Page 127	Page 129
<p>1 whether it's something that the ZHP folks 2 ought to have known about. 3 It stands here as a single 4 reference in an otherwise very lengthy 5 document. I don't know who prominence it had 6 in the industry at that time. 7 MR. SLATER: Okay. Chris, 8 let's go to Exhibit 197, please. 9 MR. GEDDIS: Is there another 10 exhibit number for that that you had 11 too? 12 MR. SLATER: Possibly 14, it's 13 the "N-N-dimethylformamide: much more 14 than a solvent" in Tetrahedron. 15 MR. FOX: You're going to a 16 different exhibit, Adam? 17 MR. SLATER: I am. The problem 18 is Chris moved so quickly before, that 19 now when he doesn't do something 20 instantaneously we all say, What's 21 going on? 22 MR. GEDDIS: What was it you 23 said, 214? 24 MR. SLATER: 14, 1-4. It was</p>	<p>1 MR. SLATER: Let's go now to 2 the third page of this article, which 3 is page 8315, please. 4 Q. It says in part, paragraph 5 number 3, "Source of carbon monoxide. DMF 6 decomposes slightly at its boiling point to 7 afford dimethylamine and carbon monoxide, 8 this reaction occurring even at room 9 temperature in the presence of some acidic or 10 basic materials. This observation has led to 11 the use of DMF as a carbonylating agent." 12 Do you see that? 13 A. I do. 14 Q. Taken together with the 15 textbook I showed you, and now I'm showing 16 you a medical -- in a scientific journal, can 17 you agree that, based on what I've shown you, 18 it was at least scientifically feasible 19 for -- and expected for ZHP to know that DMF 20 could decompose or degrade and give off 21 dimethylamine as part of this manufacturing 22 process, that they at least had to take into 23 account the possibility that that would 24 occur?</p>

Page 130

1 MR. FOX: Objection to the
2 form. Argumentative, incomplete
3 hypothetical.
4 A. I can agree that, from what
5 you've shown me, that there are references in
6 the scientific literature that are
7 potentially useful data points that should be
8 taken into account and considered in the
9 overall scheme of things. But I'm not
10 capable of judging them on the merits
11 independently, so I don't know what relevance
12 they really have.
13 BY MR. SLATER:
14 Q. What I'm just asking is, we can
15 agree that the potential decomposition of DMF
16 to give off dimethylamine, based on what I'm
17 showing you, was something that you would
18 expect ZHP to have at least been aware of as
19 a potential chemical reaction as part of the
20 zinc chloride process and take into account
21 however they chose to?
22 MR. FOX: Objection to form.
23 MR. SLATER: Let me rephrase.
24 I lost, because I was trying to finish

Page 131

1 the question and you objected. I'm
2 not criticizing because I paused, but
3 let me just ask again.
4 BY MR. SLATER:
5 Q. You would agree with me that
6 you would expect that ZHP would have at least
7 been aware of the potential degradation or
8 decomposition of the DMF to give off
9 dimethylamine, and to take that into account
10 as something that could potentially occur
11 during the zinc chloride process. Just
12 limiting it to that, would you agree with me?
13 MR. FOX: Objection to the
14 form. Asked and answered.
15 A. It's information that's out
16 there in the scientific literature. It would
17 have been appropriate for them to take a look
18 at it and give it consideration.
19 MR. SLATER: Let's take that
20 down now and go to Exhibit 211.
21 (Whereupon, Chesney Exhibit
22 Number 8 was marked for
23 identification.)
24 ///

Page 132

1 BY MR. SLATER:
2 Q. Okay. We have on the screen an
3 article titled Theoretical Investigation of
4 N-Nitrosodimethylamine Formation from
5 Nitrosation of Trimethylamine.
6 Do you see that?
7 A. Yes.
8 Q. And at the bottom of the first
9 page of the article there's an exhibit
10 sticker, Peng Dong ZHP 211. Again, I'm
11 representing to you this was utilized in Peng
12 Dong's deposition as well as Min Li's
13 deposition, which we've already established
14 you have not seen those transcripts, correct?
15 A. Correct.
16 Q. And the articles that I've
17 shown you, these scientific articles that
18 were used in those depositions, you haven't
19 seen any of these, right?
20 A. No.
21 Q. Okay. Meaning I'm correct?
22 A. Yes.
23 Q. I wasn't trying to be picky,
24 it's just sometimes the negatives on the

Page 133

1 double negatives won't be clear.
2 A. No, I have not seen this
3 article before.
4 MR. SLATER: Okay. Let's,
5 Chris, if you could just blow up the
6 Introduction, that left column, that
7 would be great.
8 Q. Okay. And let's just start out
9 at the beginning. It says, "It is well known
10 that N-nitrosamines are a class of undesired
11 industrial and environmental pollutants, many
12 of which are carcinogenic, mutagenic, and
13 teratogenic. In particular,
14 N-nitrosodimethylamine (NDMA), which is the
15 simplest dialkyl nitrosamine, has been
16 demonstrated to be a potent carcinogen to
17 various organs in animals, including liver,
18 lung, and kidney." And I just want to stop
19 there.
20 Does this comport with at least
21 what you've learned about NDMA since you were
22 retained in this matter, or from the
23 literature, from the media reports you had
24 seen before? I'm just curious if you're

<p>Page 134</p> <p>1 familiar with at least these types of 2 information about NDMA. 3 A. The carcinogenic potential, 4 yes. The detail involving the specific organ 5 systems that might be at risk, no, I haven't 6 seen much in the way of specific reference to 7 that before. 8 Q. And I neglected to ask about 9 this, but maybe I can do it real quick. 10 The importance of detecting 11 genotoxic impurities as potential 12 manufacturing process impurities, that was 13 not a novel concept in 2011, ZHP would have 14 known at that point that that was something 15 they had to be on the lookout for, right? 16 MR. FOX: Objection to form. 17 A. Be on the lookout for what? 18 BY MR. SLATER: 19 Q. For genotoxic process 20 impurities as a part of any manufacturing 21 process? 22 A. There's long been a general 23 awareness that unidentified impurities need 24 to be characterized so you know what you're</p> <p>Page 135</p> <p>1 dealing with, and then back up and look and 2 see what the implications are of those 3 materials present in your product as a result 4 of your process, and to the extent feasible 5 to quantitate them. 6 Q. And with regard to genotoxic 7 impurities which could potentially lead to 8 cancer, it's been understood that those need 9 to be focused on and they need to be 10 identified and addressed, correct? 11 MR. FOX: Objection to form. 12 A. Well, if you identify either 13 the potential or the actual occurrence of 14 this type of impurity, then certainly it's 15 important to understand it. 16 BY MR. SLATER: 17 Q. Looking now at the second 18 paragraph under the Introduction, it says, 19 "because dialkylnitrosamines are of great 20 interest in carcinogenesis, much attention 21 have been focused on their formation 22 mechanism, especially from secondary amines. 23 Consequently, NDMA is generally believed to 24 be formed from the reactions of dimethylamine</p>	<p>Page 136</p> <p>1 (DMA) and nitrosating agents, such as N2O3, 2 N2O4 and ONCl." 3 And I can represent to you that 4 N2O3 would be nitrous acid, I believe. 5 Actually I just screwed up the whole question 6 so I've got to ask it again. 7 This says, "Because 8 dialkylnitrosamines are of great interest in 9 carcinogenesis, much attention has been 10 focused on their formation mechanism, 11 especially from secondary amines. 12 Consequently, NDMA is generally believed to 13 be formed from the reactions of dimethylamine 14 (DMA) and nitrosating agents, such as N2O3, 15 N2O4, and ONCl." 16 Do you see what I just read? 17 A. Yes. 18 MR. SLATER: And let's just 19 scroll up a little bit just to the 20 authors of the article again. I want 21 to just show -- there we go. 22 Q. This article was published by 23 three authors at the College of Life Science 24 & Bioengineering at Beijing University of</p> <p>Page 137</p> <p>1 Technology in Beijing, China, and it shows 2 that it was -- in 2009 it was received, and 3 published in 2010. 4 Do you see that? 5 A. Yes. Okay. I was just looking 6 for publication date. Yes, I see that. 7 Q. Would you agree with me that 8 this demonstrates that it was certainly 9 feasible and expected for ZHP to be aware 10 that the potential DMA that could be produced 11 during the manufacturing process could react 12 with the nitrous acid to form NDMA? Would 13 you agree that this demonstrates that it's 14 certainly something that they needed to be 15 aware of and take into account in their risk 16 assessment? 17 MR. FOX: Objection to the 18 form. It's beyond the scope of his 19 expertise, as he has testified 20 repeatedly that he's not a scientific 21 expert. 22 MR. SLATER: Counsel, do you 23 want to testify? 24 MR. FOX: If you'd like me.</p>
---	---

Page 138

1 MR. SLATER: We'll do that
2 later. We do the lawyer testimony
3 later.
4 A. This is another example of the
5 kind of information I would need input from
6 somebody with the appropriate expertise to
7 fully take into consideration. I can only
8 judge this on the merits.
9 BY MR. SLATER:
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]
14 [REDACTED]
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 MR. FOX: Objection to the
22 form.
23 MR. SLATER: Okay. I think we
24 can take that one down.

Page 139

1 BY MR. SLATER:
2 Q. I'd like to ask you to assume
3 that ZHP's corporate representative witnesses
4 testified that they did not take into
5 consideration the potential degradation or
6 decomposition of DMF to yield DMA, nor did
7 they take into consideration the potential
8 reaction between DMA and nitrous acid, that
9 they didn't even take that into consideration
10 at all, they didn't think about it, they
11 didn't look at the issue, they completely
12 didn't think about that.
13 If my hypothetical is true,
14 would you agree with me that that
15 demonstrates a lack of rigor in violation of
16 GMP based on them not even taking it into
17 consideration and thinking about it?
18 MR. FOX: Objection to form.
19 A. I would not go that far until I
20 had the opportunity to ask them a simple
21 question, Why did you not, and hear what
22 their justification is.
23 BY MR. SLATER:
24 Q. What if their justification was

Page 140

1 nobody knew -- rephrase.
2 What if their justification
3 was, Nobody could have known that these
4 chemical reactions could have occurred? In
5 the face of what I've just shown you, would
6 you agree that that would show that their
7 evaluation fell below good manufacturing
8 practices?
9 MR. FOX: Objection to the form.
10 Incomplete hypothetical.
11 A. I would then ask them why they
12 took that position and what there is that's
13 different about the chemistry of their
14 process that leads them to conclude that.
15 BY MR. SLATER:
16 Q. What if they -- well, are you
17 saying you would ask them why is it that
18 you're concluding that nobody could have
19 known about these potential chemical
20 reactions in the face of publicly available
21 scientific literature, including from
22 scientists in Beijing, that you would not
23 have known what other people had readily
24 available to them?

Page 141

1 MR. FOX: Objection to the
2 form.
3 BY MR. SLATER:
4 Q. I don't understand -- I'm just
5 trying to understand why you would ask them
6 that question in the face of what I've shown
7 you.
8 A. I would -- no, I would expect
9 them to know that that information was out
10 there. But why they excluded it from
11 consideration in their particular product
12 would be what I'd like to hear their
13 explanation of. I don't know if they would
14 have such an explanation or not, but I would
15 certainly ask them, Is there anything about
16 your particular process that led you to
17 believe that information such as this would
18 not be relevant.
19 But a lack of awareness that it
20 exists or even to rule it out as important,
21 no, I would expect them to go that far at
22 least.
23 Q. As a matter of GMP, right?
24 MR. FOX: Objection to form.

<p>Page 142</p> <p>1 A. Yes.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. What if their answer to your</p> <p>4 question was, We didn't exclude it, we never</p> <p>5 even thought about it --</p> <p>6 MR. FOX: Objection to form.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. -- would that fall below GMP</p> <p>9 then?</p> <p>10 MR. FOX: Objection to form.</p> <p>11 Misstates -- or incomplete</p> <p>12 hypothetical.</p> <p>13 A. They certainly should be</p> <p>14 looking at the relevant literature to see if</p> <p>15 there's anything about what they're proposing</p> <p>16 to do in their process that poses a potential</p> <p>17 risk. So yeah, I would expect them to at</p> <p>18 least be aware of the existence of this</p> <p>19 information.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. And if their -- rephrase.</p> <p>22 If their response to your</p> <p>23 question, which I think you said your</p> <p>24 question would be, Well, why did you exclude</p>	<p>Page 144</p> <p>1 BY MR. SLATER:</p> <p>2 Q. You can answer.</p> <p>3 A. It's a concern I would have,</p> <p>4 but I would ask that the scientific experts I</p> <p>5 was working with resolve it on a peer-to-peer</p> <p>6 basis and give me their insight and their</p> <p>7 opinion.</p> <p>8 Q. Well, coming back to my</p> <p>9 question, though, since you've already agreed</p> <p>10 with me that they were required to at least</p> <p>11 know about these potential chemical reactions</p> <p>12 that could occur during the process, if you</p> <p>13 then asked them, Well, why did you not</p> <p>14 perform an actual risk assessment on whether</p> <p>15 or not these reactions were going to occur or</p> <p>16 were occurring, and they said, We never even</p> <p>17 took it into account, we didn't even think</p> <p>18 about this, we never even thought about these</p> <p>19 potential reactions, if that were to be their</p> <p>20 response, would you agree that that would</p> <p>21 show that their -- the fundamental parts of</p> <p>22 their risk assessment fell below GMP because</p> <p>23 they never even made themselves aware of</p> <p>24 these potential reactions to begin with?</p>
<p>Page 143</p> <p>1 this information from consideration, if their</p> <p>2 response was, We didn't even actively exclude</p> <p>3 it and say we're not going to consider it, we</p> <p>4 didn't even know it, because we didn't even</p> <p>5 do a research, a literature -- rephrase. Let</p> <p>6 me try to ask it clean.</p> <p>7 If you were to ask them, Why</p> <p>8 did you decide this information didn't need</p> <p>9 to be taken into account, and they said, We</p> <p>10 didn't even make a decision about whether to</p> <p>11 take it into account, we just never even</p> <p>12 knew --</p> <p>13 MR. FOX: Is that a question?</p> <p>14 BY MR. SLATER:</p> <p>15 Q. -- would I be correct that you</p> <p>16 would say, Well, your risk assessment fell</p> <p>17 below GMP because you at least should have</p> <p>18 known this information was available and made</p> <p>19 a reasoned decision as to how you were going</p> <p>20 to take it into account?</p> <p>21 MR. FOX: Objection. Misstates</p> <p>22 testimony. It's also beyond the scope</p> <p>23 of his expertise, given that he's not</p> <p>24 a scientific expert.</p>	<p>Page 145</p> <p>1 MR. FOX: Objection. Beyond</p> <p>2 the scope, incomplete hypothetical,</p> <p>3 and misstates his prior testimony.</p> <p>4 A. I'm sorry, I lost -- in all of</p> <p>5 that I lost the thread of the question. Can</p> <p>6 you restate it? I had to ask you to restate</p> <p>7 it, but please do.</p> <p>8 MR. SLATER: Just so that I</p> <p>9 don't misstate it a little differently</p> <p>10 and get another objection that might</p> <p>11 distract you, Maureen, could you read</p> <p>12 that question back, please?</p> <p>13 I'll ask the court reporter to</p> <p>14 read it back, and if I need to reask</p> <p>15 it I will again, but maybe this will</p> <p>16 be the quicker way to go.</p> <p>17 (Whereupon, the reporter read</p> <p>18 back the following:</p> <p>19 QUESTION: Well, coming back to</p> <p>20 my question, though, since you've</p> <p>21 already agreed with me that they were</p> <p>22 required to at least know about these</p> <p>23 potential chemical reactions that</p> <p>24 could occur during the process, if you</p>

Page 146

1 then asked them, Well, why did you not
 2 perform an actual risk assessment on
 3 whether or not these reactions were
 4 going to occur or were occurring, and
 5 they said, We never even took it into
 6 account, we didn't even think about
 7 this, we never even thought about
 8 these potential reactions, if that
 9 were to be their response, would you
 10 agree that that would show that
 11 their -- the fundamental parts of
 12 their risk assessment fell below GMP
 13 because they never even made
 14 themselves aware of these potential
 15 reactions to begin with.)
 16 MR. FOX: Same objection.
 17 A. I would agree that the risk
 18 assessment would have been better had they
 19 taken that into account for sure.
 20 BY MR. SLATER:
 21 Q. Well, if they told you they
 22 never took it into account, that would
 23 violate GMP. You've already told me they
 24 were required to know about this scientific

Page 147

1 information, so if they didn't even consider
 2 it that would violate GMP, right?
 3 MR. FOX: Objection to form.
 4 Misstates testimony.
 5 A. I think that's taking the
 6 concept a bit far. But they certainly -- the
 7 risk assessment would certainly be improved
 8 by a thorough literature search, and if they
 9 missed something like this that was publicly
 10 available and directly involved the type of
 11 reaction that was involved in their process,
 12 then yes, it should have been taken into
 13 account. And if it wasn't, that would be a
 14 gap in the overall risk assessment.
 15 BY MR. SLATER:
 16 Q. It would be a gap in violation
 17 of GMP, correct?
 18 MR. FOX: Objection to form.
 19 A. Whether or not it's a violation
 20 of GMP I'm not been prepared to say without a
 21 more rigorous understanding of the scientific
 22 considerations here.
 23 When you look at information
 24 like this in the literature, it may not have

Page 148

1 been created in an environment that
 2 duplicates adequately the environment that
 3 exists with respect to the process chemistry
 4 that you're dealing with, and there could be
 5 mitigating factors or things that would
 6 influence the production of NDMA in some way
 7 as to negate the risk. All that has to be
 8 taken into consideration before you can
 9 conclude what the impact of the lack of that
 10 information really was.
 11 BY MR. SLATER:
 12 Q. And what you just went through
 13 in terms of the types of questions that you
 14 might ask, you would expect that pursuant to
 15 GMP that people at ZHP would have asked
 16 themselves the same questions back at the
 17 time in 2011, right?
 18 A. Yes.
 19 MR. FOX: Objection to form.
 20 A. That I can agree to. The
 21 question is whether in 2011 the technology
 22 was adequate to make that identification, and
 23 whether there was reasonable probability that
 24 they would even find anything if they looked.

Page 149

1 Those are the two basic questions that I
 2 would need the scientific support to answer.
 3 BY MR. SLATER:
 4 Q. Assuming the answer to both of
 5 those assumptions is yes, as I've asked you
 6 to assume in the hypothetical, if they didn't
 7 ask themselves those questions that you just
 8 recited for me about how you would take into
 9 account -- how to take this into account in
 10 their risk assessment, they didn't even go
 11 through that exercise, that would fall below
 12 GMP, right?
 13 MR. FOX: Objection to form.
 14 Misstates testimony.
 15 A. That would be a flaw in the
 16 overall risk assessment for sure, yes.
 17 BY MR. SLATER:
 18 Q. In violation of GMP, right?
 19 MR. FOX: Objection to form.
 20 A. I'm not prepared to go that
 21 far. That requires a multifaceted
 22 consideration really as to what the risk is
 23 that's presented.
 24 If I may, GMP conceptually does

<p style="text-align: right;">Page 150</p> <p>1 not expect everything to be done perfectly. 2 In fact, the regulations, the finished dose 3 form regulations actually anticipate that 4 imperfections will occur, and what it calls 5 for is a thorough investigation when those 6 imperfections do occur, not that everything 7 be absolutely perfect every time. 8 If that were the case, no 9 pharmaceutical products would be produced 10 because nobody is ever 100 percent perfect. 11 That's been my experience. 12 So the question really is not 13 whether or not the risk assessment could have 14 been better, the question is was it 15 sufficiently flawed to violate GMP. And it's 16 difficult for me to take it to that level. 17 I can certainly agree that this 18 information you've highlighted would have 19 been helpful, even should have been taken 20 into consideration. But whether the fact 21 that it was not, if the testimony indeed 22 states that, constitutes a violation of GMP 23 as a further analysis, that I would not be 24 prepared to make based on this level of</p>	<p style="text-align: right;">Page 152</p> <p>1 then, sure, I could get to the point of 2 agreeing it was a violation of GMP, but not 3 based upon bits and pieces of the total 4 story. 5 BY MR. SLATER: 6 Q. When you were reading the 7 information from the FDA, were you aware that 8 the reason why nobody had been looking for 9 NDMA before was because the manufacturing 10 processes for valsartan hadn't created NDMA 11 to the FDA's knowledge before the zinc 12 chloride process was put into effect, and 13 that that's how this issue came to the FDA's 14 attention? 15 MR. FOX: Objection to form. 16 BY MR. SLATER: 17 Q. Were you aware of that? 18 A. Public statements allude to the 19 timeline on this, and the reasons why it 20 eventually did come to light. 21 What I remember from that as I 22 sit here now is that full awareness and 23 understanding didn't really occur until 24 sometime in the middle of 2018. So I</p>
<p style="text-align: right;">Page 151</p> <p>1 information. 2 BY MR. SLATER: 3 Q. If you were to assume that 4 considering that information could have 5 feasibly led to testing to see if 6 nitrosamines were being formed, if you assume 7 that, and that that testing would have shown 8 NDMA was being formed, then the failure to 9 take this into consideration in 2011 would be 10 a GMP violation, correct? 11 MR. FOX: Objection to form. 12 A. If all that was true, yes. The 13 problem is I've seen other information that 14 suggests that, at least from the FDA's public 15 statements, that suggests that that 16 information was not -- or that technology was 17 not up to speed until much later. Neither 18 the regulators nor the industry at large 19 really had that awareness. 20 So I question whether it was 21 feasible in 2011. I don't know, and I would 22 require the help of someone with the right 23 scientific expertise to convince me of that. 24 If I could be convinced of that</p>	<p style="text-align: right;">Page 153</p> <p>1 question whether it would have been something 2 the company could have anticipated or known 3 about in 2011. 4 Q. I read something in your report 5 which indicated along the lines of what 6 you've been telling me, that the FDA doesn't 7 prescribe a one size fits all GMP approach to 8 the manufacture of each product. I think 9 you've been telling me that, right? 10 A. Yes, that's true. 11 Q. And I read a couple of things 12 in your report, and I'm just going to run 13 through them. One of the things you said is 14 that the cGMP regulations describe what is to 15 be accomplished, not necessarily how. 16 I think that's the same point, 17 right? 18 A. Yes. 19 Q. And another thing you said is 20 any reasonable format that achieves the 21 desired results. 22 Again, that's another way of 23 saying the same thing, right? 24 A. Yes.</p>

Page 154

1 Q. And I think another place you
2 said -- rephrasing.
3 Another part of your report on
4 page 51 you said, As long as the approach
5 ensures that the API meets its purported or
6 represented purity and quality. That was
7 another way of you saying you have to come up
8 with an approach, it might not be the same
9 approach someone else will have, but that's
10 the outcome that you need to achieve, right?
11 MR. FOX: Objection to form.
12 A. Yes, I think in that -- sorry,
13 Tom.
14 MR. FOX: Go ahead.
15 A. I believe in that case I was
16 actually quoting an FDA compliance program to
17 illustrate that point.
18 BY MR. SLATER:
19 Q. And that point would apply to
20 what ZHP was doing in 2011 as part of its
21 risk assessment, that its approach was
22 required to ensure that the API met the
23 purported or represented purity and quality
24 of the API, correct?

Page 155

1 A. Yes.
2 Q. We know in retrospect that the
3 risk assessment failed to do so, and that the
4 API did not satisfy the represented purity
5 and quality because it was -- it contained
6 NDMA, correct?
7 MR. FOX: Objection to form.
8 Calls for speculation.
9 A. I don't believe there was any
10 specification established for NDMA at that
11 point in time because there was no
12 anticipation that it would be there.
13 BY MR. SLATER:
14 Q. That was due to the failure of
15 the risk assessment to identify the potential
16 creation of nitrosamines, correct?
17 MR. FOX: Objection to form.
18 A. In part.
19 BY MR. SLATER:
20 Q. When the valsartan was sold by
21 ZHP, it was representing that it had a
22 certain level of quality and purity, and
23 listed what the ingredients and components
24 were that were in those pills, right?

Page 156

1 A. I've never seen the labeling
2 for how it was sold, nor any representations
3 that were made to purchasers, but implicitly
4 it would be required to comply with the law,
5 certainly.
6 Q. Have you looked at the USP
7 entries for the valsartan?
8 A. The monographs and the USP?
9 Q. Yes.
10 A. I don't recall that I looked at
11 the monographs. I do have one USP citation
12 in my list of references, but I don't think
13 that was the valsartan monograph.
14 Q. You mentioned specifications
15 before, and I think we can agree that,
16 because we talked about it earlier, that one
17 of the important parts of the risk assessment
18 is to identify what are the impurities that
19 need to be specified so that you can test to
20 make sure they're below certain levels,
21 right?
22 A. Yes.
23 Q. So if the risk assessment
24 failed -- well, rephrase.

Page 157

1 We know the risk assessment
2 failed to identify the potential NDMA
3 impurity, we know that, that's why it was
4 never part of the process validation testing,
5 and that's why there was never any even
6 attempt to set a specification for NDMA,
7 right?
8 MR. FOX: Objection to form.
9 A. I think -- my understanding is
10 that that's not the only reason.
11 The other reason is there were
12 not available analytical methods that were
13 sensitive enough at the levels that
14 apparently this material was occurring to
15 enable detection at that point.
16 BY MR. SLATER:
17 Q. And I think you said earlier
18 you haven't seen Dr. Hecht's report, so
19 you're not aware of the fact that one of the
20 world's foremost experts regarding
21 nitrosamines and the use of mass spectrometry
22 has written in his report that the technical
23 ability to identify the NDMA was absolutely
24 available in 2011, that's not something that

Page 158

1 you're aware of, right?

2 MR. FOX: Objection to form.

3 Lacks foundation, argumentative.

4 A. I'm not aware of it, no.

5 BY MR. SLATER:

6 Q. If I am correct that it was

7 technically feasible for ZHP to have employed

8 technology to test for NDMA and identify the

9 NDMA in 2011, you would agree with me based

10 on all the information I've shown you that

11 they should have performed that test and they

12 should have detected the NDMA before ever

13 marketing this product, right?

14 MR. FOX: Objection to form.

15 Asked and answered, misstates

16 testimony.

17 A. That would require a series of

18 steps; that the risk analysis would recognize

19 that as a potential problem, that they had

20 the available technology or acquired it or

21 found someone to contract with to do the

22 testing, did the testing, and identified the

23 NDMA at the levels in which it was occurring.

24 And even then, you would have

Page 159

1 to take that quantitative information and

2 determine whether or not that was a health

3 risk, and if so, how severe, and to whom, and

4 all the rest of it.

5 BY MR. SLATER:

6 Q. Well, we know what happened

7 when the world found out there was NDMA in

8 the valsartan, we found out that the levels

9 that ZHP had created in its valsartan were so

10 high that the pills couldn't be sold any

11 longer, right?

12 MR. FOX: Objection to the

13 form.

14 A. The levels were such that the

15 FDA classified the recall as Class 2, which

16 is minimal risk to health, and actually

17 issued public advice to patients taking those

18 tablets or capsules to continue to take the

19 medication until they either had an

20 alternative available, or their physician had

21 switched their medication.

22 So the FDA's official advice on

23 this was keep taking your medication until

24 you have an alternative.

Page 160

1 BY MR. SLATER:

2 Q. Are you aware that the reason

3 the FDA said that is because they figured

4 it's better not to have a heart attack or

5 stroke in the next couple weeks while you go

6 to your doctor and get a new drug rather than

7 stopping the pill?

8 MR. FOX: Objection to form.

9 BY MR. SLATER:

10 Q. Let me reask.

11 Are you aware that the reason

12 the FDA said that people should keep taking

13 the pills until they can meet with their

14 doctor is because there was a concern that

15 people could suffer strokes or cardiovascular

16 episodes and die, or have massive medical

17 harm, and that they weighed that against the

18 risk of taking the pills for another couple

19 weeks while they get new medication?

20 You understand that's why the

21 FDA said that, right?

22 MR. FOX: Objection to form.

23 A. A couple weeks or however long

24 it takes.

Page 161

1 BY MR. SLATER:

2 Q. Well, I mean, the FDA was

3 making a decision, We don't want a bunch of

4 people having strokes and dropping dead all

5 over the place because they stopped taking

6 their blood pressure medications while we get

7 them onto other medications, and then the FDA

8 -- shortly after that, this stuff was

9 completely off the market, right?

10 MR. FOX: Objection to form.

11 A. It was off the market after the

12 recall was conducted, yes.

13 BY MR. SLATER:

14 Q. Certainly the FDA telling

15 people to keep taking the pills until they

16 get an alternative blood pressure medication

17 was not an endorsement of the safety of the

18 valsartan, was it?

19 MR. FOX: Objection to form.

20 A. Safety is a relative concept in

21 pharmacology. So it was a statement by the

22 FDA that the greater good was served by

23 patients continuing it until they could get

24 an alternative medication.

<p style="text-align: right;">Page 162</p> <p>1 BY MR. SLATER:</p> <p>2 Q. Was the FDA also concerned that</p> <p>3 because ZHP had such a massive part in the</p> <p>4 market that there could be a bunch of people</p> <p>5 left with no blood pressure drugs if they</p> <p>6 stopped taking it, and there could be a lot</p> <p>7 of people getting very, very sick and dying</p> <p>8 if they all stopped taking it right away?</p> <p>9 MR. FOX: Objection to form.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. Just asking if you know.</p> <p>12 A. I don't know if they raised</p> <p>13 supply chain concerns or created a potential</p> <p>14 shortage.</p> <p>15 Q. Let me go back to a question</p> <p>16 about the testing that you've talked about,</p> <p>17 of whether it was feasible to test.</p> <p>18 If ZHP had actually taken into</p> <p>19 consideration the potential chemical</p> <p>20 reactions and realized that the creation of</p> <p>21 nitrosamines including NDMA was possible, and</p> <p>22 if it wasn't feasible to test for the NDMA or</p> <p>23 other nitrosamines back in 2011, wouldn't the</p> <p>24 proper thing to do at that point be to say,</p>	<p style="text-align: right;">Page 164</p> <p>1 case, then they would not be able to</p> <p>2 manufacture by that process, they would have</p> <p>3 to come up with a different way to</p> <p>4 manufacture it where there wouldn't be the</p> <p>5 potential creation of a genotoxic impurity</p> <p>6 that you couldn't test for, correct?</p> <p>7 MR. FOX: Objection to form.</p> <p>8 A. That's a possible outcome.</p> <p>9 BY MR. SLATER:</p> <p>10 Q. That would be the -- I'm sorry,</p> <p>11 I missed your answer because I think you</p> <p>12 might have broken up.</p> <p>13 A. I'm sorry, just waiting for</p> <p>14 Tom.</p> <p>15 That -- yes, that would be a</p> <p>16 possible outcome. They could elect to hold</p> <p>17 off on the process change until that question</p> <p>18 could be answered, yes.</p> <p>19 Q. I mean, that would be --</p> <p>20 rephrase. That would be required --</p> <p>21 rephrase.</p> <p>22 At the very least, they</p> <p>23 couldn't go forward and institute that</p> <p>24 manufacturing process until they could answer</p>
<p style="text-align: right;">Page 163</p> <p>1 We can't move forward until we can test and</p> <p>2 confirm that these genotoxic impurities are</p> <p>3 not in this pill? Wouldn't that be what</p> <p>4 would be required if the testing didn't exist</p> <p>5 at the time?</p> <p>6 MR. FOX: Objection to form.</p> <p>7 Argumentative, beyond the scope.</p> <p>8 A. If there was a concern about a</p> <p>9 substantial risk that they didn't have the</p> <p>10 feasibility to address through analytical</p> <p>11 procedures due to a lack of equipment or</p> <p>12 knowledge of the method or whatever, the</p> <p>13 usual approach is to try to find someone who</p> <p>14 can assist with that line of inquiry.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. And I'm just going to play out</p> <p>17 what you've questioned me about to the end.</p> <p>18 Let's assume that they -- there</p> <p>19 was no technology available to test for NDMA</p> <p>20 or other nitrosamines at that point, even</p> <p>21 though they knew this manufacturing process</p> <p>22 very well could be creating these genotoxic</p> <p>23 impurities, if that were the case -- I'm</p> <p>24 taking your hypothetical -- if that were the</p>	<p style="text-align: right;">Page 165</p> <p>1 the question of whether or not this genotoxic</p> <p>2 impurity was in the pill, right?</p> <p>3 MR. FOX: Objection to form.</p> <p>4 Incomplete hypothetical.</p> <p>5 A. They should have taken that</p> <p>6 into consideration, and that's a decision</p> <p>7 that would have to be made in light of all</p> <p>8 the facts, and with the appropriate</p> <p>9 scientific expertise coming to bear.</p> <p>10 But yes, that's a possible</p> <p>11 decision that they could have taken at that</p> <p>12 time, to not go forward.</p> <p>13 BY MR. SLATER:</p> <p>14 Q. It would not have been --</p> <p>15 rephrase.</p> <p>16 Taking your hypothetical that</p> <p>17 there was no test in existence that could</p> <p>18 have told you whether or not this genotoxic</p> <p>19 impurity was there or not, if that was the</p> <p>20 fact, it would not have been acceptable to go</p> <p>21 forward with the manufacturing process while</p> <p>22 not knowing if there was going to be this</p> <p>23 genotoxic impurity. That would not have been</p> <p>24 permitted, correct?</p>

Page 166

1 MR. FOX: Objection to form.
2 Beyond the expertise, incomplete
3 hypothetical.
4 A. Again, I would agree if and
5 only if the weight of the science argued that
6 there was a significant risk of formation of
7 NDMA. There are literature references which
8 you've shown me that showed in a laboratory
9 setting people that identified this as a
10 potential risk that's of concern, they should
11 consider that.
12 But it would take a more
13 wholistic assessment to understand whether
14 that was a real risk, and decide accordingly
15 whether to proceed with that process change
16 at that time.
17 BY MR. SLATER:
18 Q. In retrospect you would agree
19 with me it was a real risk because it
20 happened, right?
21 MR. FOX: Objection to form.
22 Argumentative.
23 A. Well, I agree with you that it
24 happened.

Page 167

1 BY MR. SLATER:
2 Q. Okay. I wanted to just
3 establish that. If we -- if you'll assume
4 for the moment that a reasonable scientific
5 expert in this field would say, Yes, this
6 would be considered a real risk that this
7 manufacturing process could create NDMA or
8 other genotoxic impurities, if that were the
9 fact, and if your hypothetical was correct
10 that no test existed that could have measured
11 whether or not this genotoxic impurity was
12 actually being created, under those
13 circumstances you could not go forward and
14 manufacture with this process, you'd have to
15 come up with a different way to do it, right?
16 MR. FOX: Objection to form.
17 A. You should not go forward
18 unless there's a persuasive reason to believe
19 that the formation of these impurities would
20 be at such a low level that it would not
21 present a risk to human health.
22 MR. FOX: Break, Adam?
23 MR. SLATER: Sure. I was
24 losing track of the time. It's fine.

Page 168

1 BY MR. SLATER:
2 Q. Do you want to -- I don't know
3 what you want to do, Mr. Chesney, if you want
4 to take a little longer, you want to eat
5 because it's almost 1:00 o'clock, whatever
6 you want?
7 A. Well, maybe a little bit longer
8 and just grab something quick. I'm certainly
9 not one who takes a big lunch anyway.
10 Q. All right. Well, you tell me,
11 how long would you like? I'm just on my
12 second bite of my apple so far, so I'm going
13 to eat an entire apple for the next eight
14 hours.
15 A. Okay. Well, it's about
16 20 minutes of 1:00, why don't we say, I don't
17 know --
18 Q. I'm not trying to rush you.
19 Make sure you give yourself a comfortable
20 amount of time.
21 A. Ten minutes past 1:00 sound
22 okay to you?
23 Q. That sounds really good. We'll
24 shoot for that.

Page 169

1 A. All right. Fine.
2 THE VIDEOGRAPHER: The time is
3 12:38 p.m. We are off the record.
4 (Whereupon, a luncheon recess
5 was taken.)
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

<p style="text-align: right;">Page 170</p> <p>1 AFTERNOON SESSION</p> <p>2</p> <p>3 THE VIDEOGRAPHER: The time is</p> <p>4 1:24 p.m. We are back on the record.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. Okay. We are ready to resume,</p> <p>7 Mr. Chesney.</p> <p>8 Question, I read your</p> <p>9 discussion of adulteration in your report,</p> <p>10 which I hope not to have a long, drawn-out</p> <p>11 discussion about it, I think I understand</p> <p>12 your points, but we may have to come back to</p> <p>13 it a little bit. But let me ask you one</p> <p>14 question maybe to help to avoid a lot of</p> <p>15 that. So here's the question.</p> <p>16 If the zinc chloride process</p> <p>17 violated cGMP as we've discussed, if that's</p> <p>18 the case, then the valsartan API manufactured</p> <p>19 with that process would be adulterated,</p> <p>20 correct?</p> <p>21 MR. FOX: Objection to form.</p> <p>22 A. If it is determined that there</p> <p>23 is a GMP violation that is sufficient to</p> <p>24 establish adulteration under the FDCA.</p>	<p style="text-align: right;">Page 172</p> <p>1 your report, "The actions taken are, in my</p> <p>2 opinion, responsible steps that the FDA would</p> <p>3 expect of any company who had discovered and</p> <p>4 self-disclosed an issue with a distributed</p> <p>5 product."</p> <p>6 I want to ask you a couple</p> <p>7 questions about that statement, okay?</p> <p>8 A. Sure. That's on page 40. Can</p> <p>9 you tell me, I've got page 40 open on my hard</p> <p>10 copy, whereabouts are you in that?</p> <p>11 Q. The third line from the top.</p> <p>12 A. Oh, okay. All right. I see</p> <p>13 it, yes.</p> <p>14 Q. When you say that those were</p> <p>15 responsible steps that the FDA would expect</p> <p>16 of any company in that situation, those steps</p> <p>17 were legally required of ZHP, correct?</p> <p>18 MR. FOX: Objection to form.</p> <p>19 Calls for a legal conclusion.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. I'll ask the question</p> <p>22 differently.</p> <p>23 Based on your understanding of</p> <p>24 the applicable FDA regulations and statutes,</p>
<p style="text-align: right;">Page 171</p> <p>1 That's a big if.</p> <p>2 BY MR. SLATER:</p> <p>3 Q. I understand. Nobody is saying</p> <p>4 that you've agreed to all aspects of the</p> <p>5 hypothetical I gave you, but I just wanted to</p> <p>6 understand if that's the case what the</p> <p>7 consequences were, or what the implications</p> <p>8 were.</p> <p>9 And sort of -- okay. What I'm</p> <p>10 doing is looking at my outline to see if I</p> <p>11 can cut through a few things. Okay.</p> <p>12 We talked a little bit about</p> <p>13 earlier about what ZHP did when they learned</p> <p>14 about the NDMA in the valsartan. I want to</p> <p>15 talk a little more about that with you, okay?</p> <p>16 A. Okay.</p> <p>17 Q. Let me just find in your</p> <p>18 report.</p> <p>19 One of the things that you said</p> <p>20 in your report is the actions taken -- well,</p> <p>21 let me start over.</p> <p>22 With regard to what ZHP did</p> <p>23 when it learned that there was NDMA in the</p> <p>24 valsartan, you say -- this is on page 40 of</p>	<p style="text-align: right;">Page 173</p> <p>1 is it your opinion that those steps that ZHP</p> <p>2 took in June of 2018 were legally required of</p> <p>3 ZHP?</p> <p>4 MR. FOX: Same objection.</p> <p>5 A. No. These are not things that</p> <p>6 are covered by any specific FDA regulation or</p> <p>7 statutory requirement; they're just</p> <p>8 reasonable and proper things to do when a</p> <p>9 company has information of this sort.</p> <p>10 But there's nothing that I'm</p> <p>11 aware of that's an affirmative duty for ZHP</p> <p>12 to have done any of these based on a specific</p> <p>13 FDA regulation or statutory requirement.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. One of the things you told me,</p> <p>16 and it's stated in your report, is that</p> <p>17 pursuant to 21 CFR 314.81(b)(1), ZHP was</p> <p>18 required to submit a field alert report</p> <p>19 within three business days to the FDA once it</p> <p>20 had learned that there was NDMA in the</p> <p>21 valsartan, correct?</p> <p>22 A. But that's not one of the five</p> <p>23 elements that I cite here. It begins on</p> <p>24 page 39 at the bottom.</p>

Page 174

1 Q. Okay. So let's go through the
 2 five elements. Well, going back to -- I'll
 3 ask you a different question and then we'll
 4 come back to where you were.
 5 ZHP was legally required
 6 pursuant to 21 CFR 314.81(b)(1) to submit a
 7 field alert report to the FDA within three
 8 business days of learning there was NDMA in
 9 its valsartan, correct?
 10 A. Yes, with one slight
 11 modification, and that being that because
 12 this is under an abbreviated new drug
 13 application, the regulation that directly
 14 covers it is 314.98, but it reflects back to
 15 314.81 for the content. So in effect, yes.
 16 Q. Bottom line was ZHP was
 17 required to notify the FDA that there was
 18 NDMA in its valsartan within three business
 19 days of learning that, correct?
 20 A. Yes.
 21 Q. Once ZHP knew that the zinc
 22 chloride manufacturing process was creating
 23 NDMA as an impurity, was ZHP required to stop
 24 using that manufacturing process as a matter

Page 175

1 of GMP pending further evaluation?
 2 MR. FOX: Objection to form.
 3 A. Once again, no specific
 4 requirement for that, but that would be the
 5 reasonable thing to do.
 6 BY MR. SLATER:
 7 Q. Well, it's my understanding
 8 that at all times that ZHP was manufacturing
 9 valsartan with the zinc chloride process,
 10 that if it knew that NDMA was an impurity in
 11 that valsartan API, that ZHP would have had
 12 to address that situation pursuant to GMP,
 13 correct?
 14 MR. FOX: Objection to form.
 15 BY MR. SLATER:
 16 Q. Starting broad right now.
 17 A. What do you mean by "address
 18 that situation"?
 19 Q. Well, let me ask you this
 20 question.
 21 When ZHP first learned that
 22 there was NDMA in its valsartan API and that
 23 it was a process impurity, did GMP require
 24 that ZHP take any steps?

Page 176

1 MR. FOX: Objection to form.
 2 No foundation.
 3 A. It would require that they
 4 conduct a thorough investigation to determine
 5 where that was coming from, and how to
 6 control it going forward, and what to do
 7 about it in the interim.
 8 BY MR. SLATER:
 9 Q. When you say how to control it
 10 in the interim, what do you mean by that?
 11 A. Well, the steps that they took,
 12 for example, placing existing inventory on
 13 hold until the investigation was complete and
 14 the decision could be made as to what to do.
 15 Ultimately, of course, they conducted a
 16 recall, notifying customers to place a hold
 17 on valsartan API, those kinds of interim
 18 controls, while the investigation is ongoing
 19 and coming to its ultimate conclusion. Those
 20 are reasonable things to do.
 21 None of those are prescribed
 22 specifically by GMP, but they certainly are
 23 the kinds of things that responsible
 24 companies do when in this situation.

Page 177

1 Q. Well, what I'm trying to
 2 understand is what GMP required based on the
 3 documents you reviewed, based on -- to the
 4 extent you have any knowledge of any internal
 5 SOPs, I'm trying to get a idea of what GMP
 6 required when ZHP first learned that there
 7 was NDMA in its valsartan API.
 8 I think the first thing you
 9 said is it needed to do a thorough
 10 investigation to figure out why, where it's
 11 coming from, correct?
 12 A. And also the risk. And then --
 13 Q. I'm sorry, I wanted to go one
 14 step at a time just because --
 15 A. Sure.
 16 Q. I'll start over. We'll do it
 17 in small steps.
 18 A. Okay.
 19 Q. When ZHP first learned that
 20 there was NDMA in its valsartan API, GMP
 21 would have required ZHP to do an
 22 investigation to determine why is it there,
 23 where is it coming from, correct?
 24 A. Yes, and the associated risk.

Page 178

1 Q. And to evaluate the associated
 2 risk?
 3 A. Yes.
 4 Q. Once ZHP understood that this
 5 was coming from the process, the
 6 manufacturing process itself, and understood
 7 that this was a genotoxic impurity that was
 8 considered to be a probable human carcinogen,
 9 what did GMP require ZHP to do once it knew
 10 that information?
 11 MR. FOX: Objection to form.
 12 A. If feasible, quantify the
 13 levels of the compound that were present as a
 14 result of its formation during the process,
 15 and include a health hazard assessment as to
 16 what the implications are of that level of
 17 material, once they had a clear understanding
 18 of what the levels were that were occurring,
 19 whether they were just trace levels that
 20 would perhaps have a negligible or no effect,
 21 or whether they were at levels of concern.
 22 That would be the next step.
 23 BY MR. SLATER:
 24 Q. You would agree with me that

Page 179

1 knowing what you know now, the levels were at
 2 levels that would be of concern, correct?
 3 A. Right. And they agreed as
 4 well, that's why they conducted the recall.
 5 Q. And again, I'm sticking with
 6 GMP right now, so I want to just make sure
 7 we're on the same page that once ZHP
 8 understood there was NDMA in the valsartan
 9 API, it needed to do a thorough
 10 investigation, determine what was the root
 11 cause, also to evaluate the potential health
 12 hazard, quantify the levels.
 13 And then what else would have
 14 been required by GMP?
 15 MR. FOX: Objection to form.
 16 A. Exactly what they did here,
 17 which is for the quality unit to take
 18 appropriate action with respect to the
 19 material in their possession, and would have
 20 to evaluate whether a recall was necessary,
 21 which they did. And they placed the material
 22 on hold and notified their customers. They
 23 also notified the FDA.
 24 ///

Page 180

1 BY MR. SLATER:
 2 Q. Would that also have required
 3 that they stop manufacturing for the time
 4 being?
 5 A. It wouldn't have required that.
 6 Some companies in a situation like this where
 7 information is still developing and they're
 8 not sure where it's going to come out, if
 9 there's sufficient demand they may continue
 10 to manufacture at risk, but put any new lots
 11 manufactured also on hold.
 12 Other companies will look at
 13 that and say no, the risk is too high, we
 14 don't want to make that investment in the
 15 cost of goods, and they'll simply cease
 16 manufacturing until they sort the matter out.
 17 So if they continue to
 18 manufacture, they should certainly -- they
 19 would certainly not be wise to distribute any
 20 additional product made, but rather to put
 21 that on hold with the rest of it.
 22 Q. Would there have been anything
 23 else that GMP would have required of ZHP?
 24 MR. FOX: Objection to form.

Page 181

1 A. Once a final conclusion is made
 2 that the product is not in a saleable
 3 condition, then the final thing would be for
 4 the quality unit to reject the material that
 5 they still had control over and any returns
 6 they get back as a result of the recall.
 7 Some companies in a recall
 8 situation will authorize the destruction by
 9 their consignees rather than have it all
 10 returned.
 11 BY MR. SLATER:
 12 Q. And your understanding is that
 13 from all the things you've seen, that ZHP
 14 first learned that there was NDMA in its
 15 valsartan in June of 2018, is that correct?
 16 A. That's when the investigation
 17 was in its final or latter stages, and they
 18 had done some quantification, yes.
 19 Q. Did you come to an
 20 understanding of how -- well, rephrase. Did
 21 you have an -- rephrase.
 22 Did you review materials having
 23 to do with the interactions between Novartis
 24 and ZHP regarding the NDMA impurity in the

Page 186

1 dialogue with the complainant, review of
 2 information submitted by the complainant,
 3 review of production records, a variety of
 4 ways, sometimes including laboratory analysis
 5 of retained samples if that's appropriate.
 6 All of that has to be taken into
 7 consideration based on the details of the
 8 complaint.
 9 Q. One of the things ZHP would
 10 have been expected to do would have been to
 11 evaluate the manufacturing process to
 12 determine whether there was the potential
 13 creation of impurities that could explain
 14 those unknown peaks, correct?
 15 MR. FOX: Objection to form.
 16 Calls for speculation.
 17 A. Once the manufacturing process
 18 is established and being followed, there's no
 19 requirement that they go back and reconsider
 20 something like that.
 21 What they would need to do
 22 instead is to make sure the batch records
 23 reflect that the manufacturing process that
 24 was used for the batch that was the subject

Page 187

1 of the complaint was followed as required by
 2 the master form of the record.
 3 BY MR. SLATER:
 4 Q. In terms of deciding what
 5 testing to -- rephrase.
 6 One of the things ZHP had to do
 7 was determine what type of testing to perform
 8 to try to determine the explanation for those
 9 unknown peaks; that would have been part of
 10 what they should have done, correct?
 11 MR. FOX: Objection to form.
 12 A. They should have determined
 13 whether testing was even feasible or
 14 necessary, because sometimes the information
 15 that comes in from the complainant is not
 16 that you don't really need to go to testing,
 17 other times it's helpful. So it depends on
 18 the details.
 19 BY MR. SLATER:
 20 Q. Well, in retrospect we know
 21 that there were unknown peaks attributable to
 22 NDMA, and that certain testing would have
 23 disclosed the presence of NDMA. We know that
 24 in retrospect, right?

Page 188

1 MR. FOX: Objection to form.
 2 A. I'm not sure that I know that
 3 at all. First of all --
 4 BY MR. SLATER:
 5 Q. Was it in the materials you
 6 reviewed?
 7 A. From the public statements by
 8 the FDA, those analytical procedures were not
 9 fully robust until a later date for one
 10 thing, you know. So I don't know what was
 11 available at the time. We've talked about
 12 these literature references and so on.
 13 But again, this is something I
 14 would ask a subject matter expert, Was there
 15 analytical technology available that should
 16 have been used, could have been used under
 17 these circumstances to shed some light on
 18 this.
 19 But the ordinary approach with
 20 unknown peaks is to attempt to identify them
 21 qualitatively, and then once you know that,
 22 quantitate them if that's possible with
 23 existing technology.
 24 Q. When you say "qualitatively,"

Page 189

1 you're talking about figuring out what they
 2 are?
 3 A. Yeah, what is it. And then
 4 quantitatively is okay, how much is it, how
 5 much is there present, what level is it at.
 6 Q. Well, one of the things that
 7 ZHP would have had to question was, Is there
 8 a test we can perform to identify the source
 9 of those unknown peaks. They would at least
 10 have been expected by GMP to ask themselves
 11 that question, right?
 12 MR. FOX: Objection to form.
 13 A. What I have seen the scientists
 14 do is look at the unknown peaks, look where
 15 they're alluding, evaluate the size and
 16 occurrence of them, and attempt to infer from
 17 that what might be going on.
 18 If additional testing is
 19 necessary, then they do that, but I'm not the
 20 one to make that call.
 21 BY MR. SLATER:
 22 Q. I read somewhere, and I don't
 23 remember if it was in your report or in some
 24 of the ICH documents, that risk assessment is

<p style="text-align: right;">Page 190</p> <p>1 not a static process, it's a process that 2 continues through the lifecycle of the drug's 3 production and manufacture, is that correct? 4 A. I would agree with that 5 statement, yes. 6 Q. So when the unknown peaks were 7 brought to the attention of ZHP, one of the 8 things that would have been prudent for them 9 to do would have been to go back to their 10 risk assessment to determine whether it was 11 adequate to make sure they hadn't missed 12 something that could explain those unknown 13 peaks. That would have been a prudent step, 14 right? 15 MR. FOX: Objection to form. 16 Calls for speculation. 17 A. I don't know if they did that 18 or not, but they certainly could have. 19 BY MR. SLATER: 20 Q. It would have been prudent for 21 them to do so, correct? 22 MR. FOX: Objection to form. 23 A. Yes. 24 ///</p>	<p style="text-align: right;">Page 192</p> <p>1 creation of nitrosamines, and I'm asking you 2 to assume that testing, including mass 3 spectrometry, was available to test to see if 4 this was a nitrosamine peak, if the answer to 5 both of those is yes, then GMP would have 6 required ZHP to do so when those unknown 7 peaks were reported, correct? 8 MR. FOX: Objection to form. 9 A. There's a lot of ifs in that 10 hypothetical. 11 BY MR. SLATER: 12 Q. Is the answer yes? 13 A. The answer would be yes, if the 14 answer to all the ifs you just posed was also 15 yes. 16 Q. So again, this comes back to 17 the importance of identification of the 18 potential impurity being the trigger to many 19 of these cGMP functions, correct? 20 MR. FOX: Objection to form. 21 A. Yes. 22 BY MR. SLATER: 23 Q. Would you agree that as soon as 24 ZHP had internally determined that those</p>
<p style="text-align: right;">Page 191</p> <p>1 BY MR. SLATER: 2 Q. And if it was scientifically 3 feasible for ZHP to have evaluated the 4 manufacturing process, gone through the 5 chemical reactions that could have been 6 occurring, and identify that potentially 7 nitrosamines were being created, and if it 8 was technically feasible to perform a test 9 like mass spectrometry to determine whether 10 these were nitrosamines causing these unknown 11 peaks, if both of those ifs -- if the answer 12 is yes to both of those, then that would have 13 been expected by ZHP, that would have been 14 expected by GMP, correct? 15 MR. FOX: Objection to form. 16 Incomplete hypothetical. 17 A. That's the sort of question I 18 would turn to a subject matter expert to help 19 formulate. 20 BY MR. SLATER: 21 Q. I'm asking you to assume the 22 answer is yes, it would have been 23 scientifically feasible to figure out that 24 these reactions could have led to the</p>	<p style="text-align: right;">Page 193</p> <p>1 unknown peaks could be due to the formation 2 of a nitrosamine as a result of the 3 manufacturing process, that ZHP was obligated 4 to tell the complaining customers that based 5 on their analysis of the manufacturing 6 process, one explanation could be 7 nitrosamines? 8 MR. FOX: Objection to form. 9 Calls for speculation, incomplete 10 hypothetical. 11 A. There's no requirement for them 12 to notify the complainant at that stage of 13 the game. They're in the middle of an 14 investigation. They have a hypothesis 15 formed, as you've described it, they're 16 putting a hypothesis to the test, so their 17 main investigation, that would probably be a 18 premature point at the time. 19 BY MR. SLATER: 20 Q. Once ZHP actually tested its 21 hypothesis and confirmed that there was NDMA 22 forming in the valsartan as a result of the 23 manufacturing process, at that point was ZHP 24 required to notify its customers?</p>

<p style="text-align: right;">Page 194</p> <p>1 MR. FOX: Objection to form.</p> <p>2 A. Required, no. Prudent, yes.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. How about a customer that had</p> <p>5 complained and said, Please tell us what</p> <p>6 these unknown peaks represent, was ZHP</p> <p>7 required to tell those complaining customers</p> <p>8 once ZHP knew it was NDMA, that yes, those</p> <p>9 peaks were due to NDMA?</p> <p>10 MR. FOX: Objection to form.</p> <p>11 No foundation.</p> <p>12 A. Not required by GMP, but again,</p> <p>13 the sort of thing that prudent companies do,</p> <p>14 and in fact ZHP did in June of 2018.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. If ZHP knew that there was NDMA</p> <p>17 in its valsartan API and continued to sell</p> <p>18 the API and didn't tell any of its customers</p> <p>19 and didn't tell the FDA, that would be</p> <p>20 inexcusable, correct?</p> <p>21 MR. FOX: Objection to form.</p> <p>22 No foundation, argumentative, beyond</p> <p>23 the scope.</p> <p>24 A. Use of the word "inexcusable"</p>	<p style="text-align: right;">Page 196</p> <p>1 that?</p> <p>2 MR. FOX: Objection to form.</p> <p>3 Calls for speculation.</p> <p>4 A. Well, any of a number of</p> <p>5 consequences. It would depend on a variety</p> <p>6 of factors.</p> <p>7 A product can be seized. If</p> <p>8 it's domestic US channels of distribution,</p> <p>9 FDA can move for that.</p> <p>10 FDA can seek an injunction to</p> <p>11 cause a company to cease and desist violative</p> <p>12 conduct.</p> <p>13 They can deal with it as they</p> <p>14 did in this case with a warning letter, which</p> <p>15 is a lesser way of handling it.</p> <p>16 There are a number of other</p> <p>17 possibilities, depending on the</p> <p>18 circumstances. And whether it's in domestic</p> <p>19 commerce or coming in from abroad would</p> <p>20 change the equation as well.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. Well, here we're talking about</p> <p>23 API that was coming in from China.</p> <p>24 A. Right.</p>
<p style="text-align: right;">Page 195</p> <p>1 is a little inflammatory. I think if they</p> <p>2 had knowledge that a product posed a danger</p> <p>3 to health and didn't do anything about it,</p> <p>4 that would certainly be inappropriate, and</p> <p>5 they could potentially be in violation of the</p> <p>6 Act for other reasons other than GMP as well.</p> <p>7 BY MR. SLATER:</p> <p>8 Q. What could they potentially be</p> <p>9 in violation of under the Act, aside from</p> <p>10 GMP?</p> <p>11 A. If --</p> <p>12 MR. FOX: Objection to the</p> <p>13 form. Calls for a legal conclusion.</p> <p>14 BY MR. SLATER:</p> <p>15 Q. You can answer.</p> <p>16 A. Okay. If they are aware that a</p> <p>17 product contains a contaminant that poses an</p> <p>18 actual or potential danger to health, and</p> <p>19 tell no one and continue to ship it anyway,</p> <p>20 that could be construed later, after</p> <p>21 evaluation of all the facts, as having</p> <p>22 shipped a contaminated and, therefore,</p> <p>23 adulterated product in interstate commerce.</p> <p>24 Q. What are the consequences for</p>	<p style="text-align: right;">Page 197</p> <p>1 Q. If it turned out that ZHP knew</p> <p>2 that its zinc chloride manufacturing process</p> <p>3 was creating NDMA in the API, and ZHP despite</p> <p>4 that knowledge continued to sell the API and</p> <p>5 not inform any of its customers or any</p> <p>6 regulatory authorities and kept that</p> <p>7 knowledge secret and did so for months, that</p> <p>8 would be a violation, I would assume, of the</p> <p>9 Food, Drug, Cosmetic Act, correct?</p> <p>10 MR. FOX: Objection.</p> <p>11 Hypothetical, no foundation.</p> <p>12 MR. SLATER: You know what,</p> <p>13 Counsel, you can have your -- you have</p> <p>14 your standing objection, because you</p> <p>15 give it to every question, I'm not</p> <p>16 going to make you keep saying it. I</p> <p>17 want to just get through this.</p> <p>18 MR. FOX: It's beyond the scope</p> <p>19 of his opinion.</p> <p>20 MR. SLATER: I'm not so sure it</p> <p>21 is.</p> <p>22 A. Okay. Once again let's be</p> <p>23 clear on what the question is, Mr. Slater.</p> <p>24 MR. SLATER: I'm going to ask</p>

Page 198

1 Maureen, if you could read it back.
2 It worked well the first time, so try
3 the second time.
4 (Whereupon, the reporter read
5 back the following:
6 QUESTION: If it turned out
7 that ZHP knew that its zinc chloride
8 manufacturing process was creating
9 NDMA in the API, and ZHP despite that
10 knowledge continued to sell the API
11 and not inform any of its customers or
12 any regulatory authorities and kept
13 that knowledge secret and did so for
14 months, that would be a violation, I
15 would assume, of the Food, Drug,
16 Cosmetic Act, correct.)
17 A. One thing that's missing from
18 the fact set that you put forth is how much
19 of the NDMA is present, whether it's at
20 miniscule trace amounts or amounts that could
21 potentially pose a hazard to health, and that
22 would be necessary for me to give an opinion.
23 I would also need to know once
24 the amounts were quantified what the medical

Page 199

1 opinion is in terms of the health hazard that
2 would be necessary. Because if something is
3 present at very minuscule trace amounts that
4 pose no risk whatsoever, then that could
5 result in a different answer.
6 BY MR. SLATER:
7 Q. Do you know the amounts that
8 were found in ZHP's API? Did you have a
9 chance to see that?
10 A. I have.
11 Q. Those amounts.
12 MR. FOX: Object to form.
13 A. Yeah, those amounts are
14 concerning. And again, there are a lot -- a
15 string of ifs in a row here. If this was
16 going on, if they were fully aware of it, if
17 they didn't notify the FDA, if they didn't
18 notify their customers, if they continued to
19 sell it, and so on, then yes, that could be
20 construed as a violation of the Food, Drug &
21 Cosmetic Act. I don't want to give a legal
22 opinion here.
23 The fact is, as my report
24 relates, that's not what they did in 2018.

Page 200

1 BY MR. SLATER:
2 Q. When you say that could be a
3 violation of the Food, Drug, Cosmetic Act,
4 could that be something that could rise to
5 the level of being criminal?
6 MR. FOX: Objection to the
7 form. You're asking him for a legal
8 opinion.
9 MR. SLATER: He's your expert
10 who cited to regulations all over the
11 report. I think he's competent to
12 talk about the legal implications of
13 the conduct of your client.
14 MR. FOX: And I think he did
15 that in the report. You have my
16 objection.
17 MR. SLATER: I appreciate it.
18 BY MR. SLATER:
19 Q. You can answer.
20 A. Any decision to go forward with
21 a criminal prosecution would go even beyond
22 the scientific multidisciplinary process that
23 I mentioned. This is hence my reluctance.
24 [REDACTED]

Page 201

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]
14 [REDACTED]
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 [REDACTED]

Page 210

1 Do you see that?

2 A. Yes.

3 Q. Okay. What I would like now to

4 do is go to -- now, looking at the bottom of

5 that paragraph, Dr. Lin points out, "However,

6 after the improvement, there is an unknown

7 impurity of about 0.544 percent at 26 minutes

8 in the crude irbesartan, and it is the

9 largest impurity in the irbesartan crude

10 product."

11 Do you see that?

12 A. Yes.

13 [REDACTED]

14 [REDACTED]

15 [REDACTED]

16 [REDACTED]

17 [REDACTED]

18 [REDACTED]

19 [REDACTED]

20 [REDACTED]

21 [REDACTED]

22 MR. SLATER: Let's go now to

23 the next page, please, Chris, the top

24 of the second page.

Page 211

1 Q. At the top of the next page

2 Dr. Lin states, "Through the secondary mass

3 spectrometry analysis, it can be inferred

4 that the extra NO substituent is in the

5 cyclic compound fragment, and it is very

6 likely that it is an N-NO" -- which would be

7 an N-nitroso -- "compound; it is similar to

8 the N-nitrosodimethylamine that occurs in

9 valsartan when quenched with sodium nitrite,

10 and its structure is very toxic." Then it

11 says, "Its possible formation route is shown

12 as follows:"

13 Do you see what I just read?

14 A. Yes.

15 Q. Were you aware before right now

16 that at least as of July 27, 2017, ZHP knew

17 internally that there was NDMA in valsartan,

18 and that the mechanism that was creating it

19 occurred when the valsartan was quenched with

20 sodium nitrite during the manufacturing

21 process?

22 MR. FOX: Objection to the

23 form. Misstates the document.

24 A. I can't conclude that based on

Page 212

1 what you've read up to this point in time.

2 BY MR. SLATER:

3 Q. Okay. This e-mail is dated

4 July 27, 2017.

5 A. No, the date is not in

6 question. But I can't conclude from what

7 I've heard so far that this suggests that

8 this material is actually in finished

9 valsartan.

10 It talks about being in crude

11 irbesartan, and at some stage of production

12 in valsartan. I have no idea how much more

13 synthesis or purification either of those

14 compounds are supposed to go through as

15 they're being manufactured and whether that

16 would remediate this or not.

17 That's exactly the kind of

18 scientific analysis that I would defer to

19 others and would require collaboration on.

20 Q. Okay. I hadn't asked a

21 question at that point, but I appreciate you

22 telling me where you wanted to take this.

23 But let me go back now to what I want to ask

24 you.

Page 213

1 This e-mail is dated July 27,

2 2017. It's written by Jinsheng Lin, who we

3 [REDACTED]

4 [REDACTED]

5 [REDACTED]

6 [REDACTED]

7 [REDACTED]

8 We went through that just a few moments ago,

9 correct?

10 A. Yes.

11 [REDACTED]

12 [REDACTED]

13 [REDACTED]

14 [REDACTED]

15 [REDACTED]

16 [REDACTED]

17 [REDACTED]

18 [REDACTED]

19 [REDACTED]

20 [REDACTED]

21 [REDACTED]

22 [REDACTED]

23 [REDACTED],

24 [REDACTED]

Page 214

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 Q. What I'm asking you is -- so
13 we've established that. Now let's go to my
14 next question.
15 In this e-mail Dr. Lin, whose
16 responsible was to understand and discover
17 such root causes, states that what was being
18 seen in the irbesartan "is similar to the
19 NDMA that occurs in valsartan when it's
20 quenched with sodium nitrite."
21 Do you see that? Just asking
22 if you see those words.
23 A. I do.
24 [REDACTED]

Page 215

1 [REDACTED]
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 Q. And in this e-mail, Dr. Lin
13 compares what is being seen in this
14 irbesartan that they're experimenting with
15 and says that what they're seeing is similar
16 to the NDMA that occurs in valsartan when
17 quenched with sodium nitrite. He's stating a
18 comparison to what -- according to the words
19 on this page -- what he knows to occur in the
20 valsartan when it's quenched with sodium
21 nitrite, which you'll agree with me is a true
22 statement because that was the ultimate root
23 cause ultimately disclosed to the world,
24 correct?

Page 216

1 MR. FOX: Objection to form.
2 The document speaks for itself.
3 A. I'm still not certain about the
4 timeline here, but I mean, it says what it
5 says. So certainly I'm not quarreling with
6 the fact that the words are there.
7 But whether that aligns to what
8 the other documents I reviewed say in terms
9 of when that determination was made, my
10 memory is the final determination that they
11 based the recall on was not made until 2018,
12 which would have been approximately a year
13 more or less after this was done.
14 So I'm not sure when the
15 gentleman makes this statement whether he's
16 basing that on a final conclusion, a
17 speculation, a work in progress, or what that
18 is. It says what it says.
19 But beyond that, I don't know.
20 BY MR. SLATER:
21 Q. Well, you know from the
22 materials you were provided that what he says
23 here is the root cause for the creation of
24 NDMA.

Page 217

1 A. Was eventually determined to
2 be.
3 Q. Okay. And he was speaking to
4 the root cause in July of 2017. That's what
5 it says right here, right?
6 MR. FOX: Objection to form.
7 The document speaks for itself. Stop
8 trying to put words in his mouth.
9 BY MR. SLATER:
10 Q. That's correct, right,
11 Mr. Chesney?
12 A. It says what it says.
13 Q. You were not shown this
14 document or told about this e-mail by the
15 people who retained you, is that correct?
16 A. This is the first time I've
17 seen it.
18 Q. And you saw the list of people
19 on the first page that this was sent to. So
20 this was not one person hoarding this
21 information; it was shared with multiple
22 people within the company. I showed you
23 that, correct?
24 A. You showed me the list that it

Page 218

1 was supposedly sent to, yes.
2 Q. If ZHP knew, as reflected in
3 this document, that there was NDMA in
4 valsartan as of July 2017, all the things
5 that you said that ZHP was required to do in
6 June of 2018, you would say all those things
7 were required to be done as of July 2017 when
8 ZHP knew this, correct?
9 MR. FOX: Objection to the
10 form. Calls for speculation.
11 A. What we have in this document
12 is a side statement in one sentence to this
13 information. I don't know what's behind
14 that, what the writer meant, particularly in
15 Chinese -- I assume this was originally
16 written in Chinese -- when he crafted this
17 statement, what -- how deep his knowledge or
18 understanding of that was or whether that was
19 a speculative or off-the-cuff remark.
20 It's really very difficult to
21 make any definitive conclusion from this
22 about what the company actually knew and how
23 many people knew it in 2017.
24 He's making an -- I guess you'd

Page 219

1 call it at minimum an allegation, or a
2 suggestion maybe is a better way to put it,
3 that this is the case. What the facts are
4 behind that and how well-known they are, I
5 have no idea.
6 BY MR. SLATER:
7 Q. With all due respect, that's
8 not what I asked you, to give me every reason
9 that you could come up with why someone might
10 want to try to undercut the statement.
11 That's not what I asked you. So let's go
12 back to my question.
13 If, as stated in this document,
14 ZHP knew that there was NDMA in the valsartan
15 and it was a process impurity that was being
16 created when the sodium nitrite quenching
17 step occurred as part of the zinc chloride
18 process, then everything you said ZHP was
19 required to do in June of 2018 would be
20 transferred back to July of 2017, or whenever
21 earlier date they knew this, and all those
22 things would have been required at that time,
23 correct?
24 MR. FOX: Objection to the

Page 220

1 form. Lack of foundation, incomplete
2 hypothetical, calls for speculation.
3 A. If they knew it, yes.
4 BY MR. SLATER:
5 Q. If they knew as of at least
6 July 27th -- rephrase.
7 If ZHP knew at least as of July
8 27, 2017 that there was NDMA in the
9 valsartan, and kept that secret and didn't
10 tell any customers or any regulators until
11 Novartis came to them and forced them to
12 disclose this information in June of 2018,
13 that would be a violation of the Food, Drug
14 and Cosmetic Act, correct?
15 MR. FOX: Objection to form.
16 A. It would if it was offered for
17 importation into the United States, yes.
18 BY MR. SLATER:
19 Q. We know that ZHP was selling
20 its valsartan with NDMA in it right through
21 until the recall occurred in June or July of
22 2018, right?
23 MR. FOX: Objection to the
24 form.

Page 221

1 A. I haven't looked at their sales
2 and distribution records. I know only that
3 they had product on the market when they
4 conducted the recall, or there wouldn't have
5 been anything to recall.
6 MR. FOX: Adam, is there a
7 reason why you're not appearing on any
8 of these screens?
9 MR. SLATER: Is there a reason
10 I'm not appearing? I'm looking right
11 at myself.
12 MR. FOX: Okay.
13 MR. SLATER: I'm right below
14 Mr. Chesney, where I belong.
15 THE WITNESS: I can see him.
16 MR. SLATER: He's sitting right
17 on my -- he's got his feet right on my
18 shoulders right now.
19 A. Actually you're at the bottom
20 on my list, but I can see you.
21 MR. SLATER: I'm in here.
22 MR. FOX: Okay. I found you.
23 BY MR. SLATER:
24 Q. Okay. If, in fact, ZHP knew at

<p style="text-align: right;">Page 222</p> <p>1 least as of July 27, 2017 that there was NDMA 2 in the valsartan and didn't tell its 3 customers and didn't tell any regulatory 4 authorities and just continued to sell the 5 product, that would be a very serious 6 violation of the Food, Drug and Cosmetic Act, 7 correct? 8 MR. FOX: Objection to form. 9 Argumentative, lacks foundation. 10 A. It would be of great concern if 11 indeed that's true, but I don't know that it 12 is. 13 BY MR. SLATER: 14 Q. In terms of your ability to 15 form an opinion in this case, this is the 16 type of information you would have expected 17 to have been provided when you were provided 18 materials by counsel, correct? 19 MR. FOX: Objection to the 20 form. 21 A. If I had been provided this 22 information, it would have raised certain 23 questions in my mind. I would have referred 24 those to scientific subject matter experts,</p>	<p style="text-align: right;">Page 224</p> <p>1 APIs. That's additional important 2 information, right? 3 MR. FOX: Objection to the 4 form. 5 A. It also characterizes the 6 findings up above as not confirmed and 7 speculative. 8 BY MR. SLATER: 9 Q. The speculated structure is 10 talking about what was being seen in the 11 irbesartan, which was something they were 12 working on to try to work on that process to 13 manufacture it. They're not speculating 14 about there being NDMA in valsartan; that's 15 not stated as speculative at all, correct? 16 MR. FOX: Objection to form. 17 The document speaks for itself. 18 MR. SLATER: Counsel, you have 19 to stop, with all due respect, making 20 a document speaks for itself 21 objection. I would appreciate it if 22 it would stop. I know you're new to 23 this litigation, but the Special 24 Master has instructed that that</p>
<p style="text-align: right;">Page 223</p> <p>1 but I would have taken note of it. 2 BY MR. SLATER: 3 Q. Let's go down a little further 4 in this e-mail. 5 After the pictures of the 6 potential formation route of the nitrosamine 7 impurity in the irbesartan, the second 8 paragraph under that says, "If it is 9 confirmed as the above speculated structure, 10 then its toxicity will be very strong, and 11 there will be an extremely high GMP risk. 12 This is a common problem in the production 13 and synthesis of sartan APIs. It is 14 recommended to improve other quenching 15 processes (such as NaClO) along with the 16 optimization of the valsartan sodium azide 17 quenching process." 18 Do you see that? 19 A. I do. 20 Q. So this provides further 21 information about the depth of understanding 22 by ZHP as of July 2017, because this shows 23 that they knew that this is a common problem 24 in the production and synthesis of sartan</p>	<p style="text-align: right;">Page 225</p> <p>1 objection should not be made. 2 You don't have to take my word 3 for it, I'm just trying to help. 4 BY MR. SLATER: 5 Q. Can you answer the question, 6 please? 7 A. I'm just taking a minute to 8 read it here. 9 (Witness reviewing document.) 10 A. I'm having trouble from these 11 isolated paragraphs here making a link back 12 to valsartan, frankly. I hear what you're 13 saying, but I'm not able to get there based 14 on what it says right here. 15 Q. I'll ask you a different 16 question then. 17 You see the sentence that says, 18 "This is a common problem in the production 19 and synthesis of sartan APIs"? Do you see 20 that sentence? 21 A. I do. 22 Q. That's not phrased as something 23 he's speculating about; that's being stated 24 as fact in this e-mail. That's how it reads,</p>

Page 226

1 right?
2 A. Yes.
3 MR. FOX: Objection to the
4 form.
5 BY MR. SLATER:
6 Q. Did you say yes?
7 A. Yes.
8 Q. And we know in retrospect that
9 this was a common problem in the production
10 and synthesis of sartan APIs, which is why
11 ultimately it turned out that other
12 manufacturing processes were implicated in
13 irbesartan and losartan, that there were
14 recalls of those drugs as well. That was
15 ultimately learned, correct?
16 MR. FOX: Objection to form.
17 A. Yes.
18 BY MR. SLATER:
19 Q. And in fact, Dr. Lin makes the
20 responsible recommendation to improve the
21 other quenching processes along with the
22 optimization of the valsartan sodium azide
23 quenching process. That's the responsible
24 thing to say when you realize that your

Page 227

1 manufacturing process is creating a genotoxic
2 impurity, in this case NDMA, correct?
3 MR. FOX: Objection to the
4 form.
5 A. You're talking about the last
6 paragraph here.
7 Okay. I'm sorry, but I was
8 catching up with you by reading this in a
9 little more depth, could you either repeat
10 the question or have it read back to me,
11 please?
12 BY MR. SLATER:
13 Q. Sure.
14 It was responsible for Dr. Lin
15 to state, as he did, that he was recommending
16 that they improve the other quenching
17 processes such as NaCIO, along with the
18 optimization of the valsartan sodium azide
19 quenching process, because of the fact that,
20 as he stated, this is a common problem in the
21 production and synthesis of sartan APIs.
22 That's a responsible recommendation, right?
23 A. Yes, it is.
24 Q. In the last paragraph he

Page 228

1 states, "I've also attached a patent of a
2 2013 sodium azide NaCIO quenching method by
3 Zhejiang Second Pharma Co., Limited. They
4 proposed that the use of NaNO2 quenching will
5 result in the formation of N-NO impurities,"
6 which is N-nitroso impurities. "At the same
7 time, they used ZHP's crude Valsartan in
8 their LC-MS test" -- that would be liquid
9 chromatography-mass spectrometry -- "and
10 detected this impurity. This indicates that
11 other companies have paid attention to the
12 quality problem very early on. So leaders
13 please pay attention to this issue."
14 Do you see that paragraph I
15 just read?
16 A. Yes.
17 Q. Dr. Lin's statement to these
18 other executives -- rephrase.
19 Dr. Lin's statement that other
20 companies are aware of this quality problem,
21 and giving an example going back to 2013,
22 that's significant, isn't it?
23 MR. FOX: Objection to form.
24 A. It's my understanding that at

Page 229

1 that point in time other companies had not
2 conducted recalls or taken any market action
3 with respect to the issue, so it sounds to me
4 like it was something the industry was in the
5 process of coming to an understanding of at
6 that time.
7 BY MR. SLATER:
8 Q. Most important -- rephrase.
9 At the very end he says, "So
10 leaders please pay attention to this issue."
11 That is a very responsible thing to say in
12 this e-mail, alerting the others that receive
13 this e-mail of this situation with the
14 creation of NDMA and the fact that it's a
15 common problem in the production and
16 synthesis of sartan APIs. It's responsible
17 for him to tell the leaders in his company to
18 take note of this situation, right?
19 A. Yes.
20 MR. FOX: Objection to form.
21 BY MR. SLATER:
22 Q. And in fact, the leaders of the
23 company, right up to the highest executive,
24 would have the ultimate responsibility for

Page 230

1 this quality problem, right?

2 MR. FOX: Objection to form.

3 A. Yes.

4 BY MR. SLATER:

5 Q. And you've actually written on

6 that subject and published on that subject,

7 correct?

8 A. Yes.

9 Q. You would agree with me as a

10 matter of GMP that the information in this

11 e-mail could not be ignored; it needed to be

12 aggressively evaluated by the so-called,

13 quote-unquote, leaders as soon as it was

14 brought to their attention, right?

15 MR. FOX: Objection to form.

16 A. Yes.

17 BY MR. SLATER:

18 Q. And we know in retrospect that

19 what Dr. Lin said about the valsartan

20 quenching creating the NDMA and this being a

21 common problem in the production and

22 synthesis of sartan APIs, we know in

23 retrospect he was 100 percent correct about

24 those statements. You've seen that in the

Page 231

1 materials you've reviewed for this case,

2 right?

3 MR. FOX: Objection to form.

4 Argumentative.

5 A. Ultimately that information was

6 developed, yes.

7 BY MR. SLATER:

8 Q. Are you stunned to see this

9 e-mail, and to see that this information was

10 being circulated within ZHP as of July 2017?

11 Because you said it's the first time you've

12 become aware of that.

13 MR. FOX: Objection to form.

14 BY MR. SLATER:

15 Q. Are you stunned, shocked,

16 surprised? What word would you put on it?

17 A. I wouldn't say stunned. It

18 sounds to me like an appropriate notification

19 based on some information that is outlined in

20 the e-mail.

21 It's a few months before --

22 actually about -- let's see here, about 10 or

23 11 months before the recall, and these things

24 are -- complex scientific issues like this

Page 232

1 don't get resolved overnight.

2 I don't know what was done

3 about this, whether this was a triggering

4 point for further work that culminated in the

5 notification to FDA and the recall, or what.

6 But it certainly is responsible

7 for Dr. Lin to have made this notification,

8 and it looks like he made it to the right

9 people.

10 Q. We know, again in retrospect,

11 that what Dr. Lin said is accurate, and we

12 know that he must have had a way to know it

13 because -- well, rephrase.

14 You're certainly not taking the

15 position that he just came up with this out

16 [REDACTED]

17 [REDACTED]

18 [REDACTED]

19 [REDACTED]

20 [REDACTED]

21 [REDACTED]

22 [REDACTED]

23 MR. FOX: Objection.

24 MR. SLATER: Chris, let's go to

Page 233

1 the article in the Quality Management

2 Essentials publication that I just

3 mentioned a moment ago indirectly,

4 please.

5 And I'm not sure what exhibit

6 number would this be for the record,

7 if anybody knows.

8 MR. GEDDIS: That would be

9 Exhibit 5.

10 (Whereupon, Chesney Exhibit

11 Number 11 was marked for

12 identification.)

13 MR. FOX: Which exhibit is this

14 on the screen?

15 MR. SLATER: I think I was just

16 told Exhibit 5.

17 MR. FOX: So this has not been

18 used before.

19 MR. SLATER: This has not been

20 used before.

21 BY MR. SLATER:

22 Q. And you recognize this

23 publication, Quality Management Essentials,

24 Expert Advice on Building a Compliant System?

<p style="text-align: right;">Page 234</p> <p>1 You recognize this publication from 2018, 2 correct?</p> <p>3 A. I don't recognize the artwork, 4 but I recognize the title, yes.</p> <p>5 Q. And if we go to the third page, 6 the Table of Contents, we can see that you 7 actually wrote an article that was included 8 in this publication titled Executive 9 Responsibility for Quality, correct?</p> <p>10 A. Yes, that's correct.</p> <p>11 Q. Let's go to your article which 12 comes right after that. And this is 13 titled -- rephrase.</p> <p>14 Your article is titled 15 Executive Responsibility for Quality, and I 16 want to go to the section titled Importance 17 of Quality just below that.</p> <p>18 MR. SLATER: Chris, could you 19 make it a little bigger, please?</p> <p>20 Perfect.</p> <p>21 A. That's fine.</p> <p>22 Q. This says, "Importance of 23 Quality.</p> <p>24 "Executive commitment to</p>	<p style="text-align: right;">Page 236</p> <p>1 authorities that they knew there was NDMA in 2 the valsartan because they were so enamored 3 with the profits they were making and put 4 that ahead of the safety of people using 5 those pills, that would be reprehensible, 6 right?</p> <p>7 MR. FOX: Objection to the 8 form. Argumentative, no foundation, 9 beyond the scope of his expertise.</p> <p>10 A. It would be of great concern, 11 yes.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. It would be reprehensible, 14 right?</p> <p>15 MR. FOX: Objection. Same 16 objection.</p> <p>17 A. That's a value judgment word. 18 I prefer more precise terminology. But it 19 would not be a good thing.</p> <p>20 BY MR. SLATER:</p> <p>21 Q. Going down a little further to 22 the fourth full paragraph under Importance of 23 Quality, there's a paragraph that says, "For 24 these reasons, quality assurance (QA) and GMP</p>
<p style="text-align: right;">Page 235</p> <p>1 quality in the pharmaceutical industry is 2 critical, not only to ensure continuing 3 profitability of the company, but also for 4 the safety and well-being of patients and to 5 meet the needs of healthcare providers who 6 prescribe and use pharmaceutical products 7 every day."</p> <p>8 That's what you wrote, correct?</p> <p>9 A. Yes.</p> <p>10 Q. The primary concern has to 11 always be the safety and well-being of 12 patients, right?</p> <p>13 A. Yes.</p> <p>14 Q. It would never be acceptable 15 for ZHP or any other company to place profits 16 over safety, right?</p> <p>17 MR. FOX: Objection to form.</p> <p>18 A. I agree with that.</p> <p>19 BY MR. SLATER:</p> <p>20 Q. For example, if it turned out 21 that ZHP was making so much money with the 22 zinc chloride process to manufacture 23 valsartan API that they chose to keep secret 24 from its customers and the regulatory</p>	<p style="text-align: right;">Page 237</p> <p>1 compliance may be viewed differently in the 2 pharmaceutical industry than in those 3 industries where a reputation for high 4 quality drives sales. Quality assurance may 5 be viewed as a 'cost of doing business' or an 6 internal 'police department' issuing 7 directives that delay or prevent product 8 release. That viewpoint can result in a low 9 priority being assigned to quality operations 10 and resourcing, which can lead in turn to 11 quality problems, regulatory difficulties, 12 unnecessary expense, adverse publicity, 13 lawsuits and investor disappointment. All 14 these consequences are preventable if 15 executive managers understand the importance 16 of the quality assurance function and treat 17 it as a critical business operation just like 18 other critical areas, such as strategic 19 planning, financial management and others."</p> <p>20 That's what you wrote because 21 you believed it to be true, correct?</p> <p>22 A. Yes, sir.</p> <p>23 Q. Let's go now to the next page. 24 There's a heading that says Regulatory</p>

<p style="text-align: right;">Page 238</p> <p>1 Considerations. And you wrote, "In addition 2 to the business benefits, health regulatory 3 agencies around the world both require and 4 expect top management to support a strong 5 quality assurance function for their 6 companies." 7 Top management would include, 8 for example, the chairman of ZHP, Mr. Baohua 9 Chen; he would fall within the context of top 10 management, right? 11 A. Yes. 12 MR. FOX: Objection. 13 I'm sorry, Adam, I didn't hear 14 the name that you mentioned. 15 MR. SLATER: I said Baohua 16 Chen. Mr. Baohua Chen. 17 BY MR. SLATER: 18 Q. You then go through, after 19 introducing this section, a couple of cases 20 from the US Supreme Court that addressed the 21 executive responsibility for certain 22 regulatory violations, correct? 23 A. Yes. 24 Q. The first case you talk about</p>	<p style="text-align: right;">Page 240</p> <p>1 doctrine. It applies to those who, in the 2 words of the Court, '...stand in a 3 responsible relationship to the acts of the 4 corporation." 5 And again, you stated this 6 because you're cautioning the executives in 7 pharmaceutical companies to take their 8 quality obligations very seriously, right? 9 A. Yes. 10 Q. You then talk about the Park 11 case, US v. Park, and you say in part, "Like 12 Mr. Dotterweich, Mr. Park defended himself by 13 claiming that he was not involved in the 14 conduct that violated the law and that he had 15 delegated authority to 'dependable 16 subordinates' he trusted to do the right 17 thing." 18 And a little further down you 19 actually quote from the majority opinion from 20 the Supreme Court stating, "The Act imposes 21 not only a positive duty to seek out and 22 remedy violations when they occur but also, 23 and primarily, a duty to implement measures 24 that will ensure that violations will not</p>
<p style="text-align: right;">Page 239</p> <p>1 is US versus Dotterweich where you say that 2 "Mr. Dotterweich's company, Buffalo 3 Pharmacal, was inspected by the FDA, 4 resulting in direct adulteration and 5 misbranding findings. The FDA criminally 6 prosecuted Mr. Dotterweich and the company, 7 charging that as president, he was ultimately 8 responsible for the company's actions and 9 therefore should be found guilty of violating 10 the law." 11 And you put that in the article 12 because you found that to be a significant 13 case and a significant cautionary tale, 14 correct? 15 A. Yes. 16 Q. You said, "Following a District 17 Court case and subsequent appeal, the Supreme 18 Court ruled on his case and concluded that as 19 president, he could be held responsible for 20 the acts of the corporation even though he 21 did not know of the violations and did not 22 intend for them to occur. This has become 23 known in the US as the Doctrine of Strict 24 Liability, or 'Responsible Corporate Officer'</p>	<p style="text-align: right;">Page 241</p> <p>1 occur. 2 "The requirements of foresight 3 and vigilance imposed on responsible 4 corporate agents are beyond question 5 demanding and even onerous, but they are no 6 more stringent than the public has the right 7 to expect. We are satisfied that the Act 8 imposes the highest standard of care and 9 permits conviction of responsible corporate 10 officials, who in light of this standard of 11 care, have the power to prevent or correct 12 violations." 13 And you quoted that language 14 because you felt it to be, again, not only a 15 cautionary tale, but right on point to get 16 the attention of executives, correct? 17 A. That's right. 18 Q. When you talk about demanding 19 and even onerous obligations and the highest 20 standard of care, those statements would 21 apply to ZHP, too, right, and their 22 executives, correct? 23 MR. FOX: Objection to form. 24 Calls for conclusion.</p>

<p style="text-align: right;">Page 242</p> <p>1 A. In my opinion they apply to 2 anyone in the FDA-regulated industries. 3 BY MR. SLATER: 4 Q. Looking now on page 5, if you 5 could. Towards the bottom, you provide at 6 the bottom, you say, "some general 7 suggestions that apply to all companies in 8 this industry, regardless of size or 9 complexity." 10 And number 1, you say, 11 "Executive managers must recognize the 12 criticality of a strong quality assurance 13 organization and quality system to patient 14 safety and to the company's business 15 success." 16 And that's an important 17 foundational point, right, that QA has to be 18 prioritized? Right? 19 A. Yes. 20 Q. Looking at number 2, "Quality 21 management must be seen as similar to other 22 critical business management activities 23 executives participate in, such as strategic 24 planning, budget management, succession</p>	<p style="text-align: right;">Page 244</p> <p>1 just words on paper." 2 I wanted to ask you about the 3 "words on paper" part, because that jumped 4 out to me when I read this. 5 That's an important point to 6 you, that it's not enough just to put these 7 policies in writing, but you actually have to 8 be committed to following through with them 9 and taking these obligations seriously, 10 right? 11 MR. FOX: Objection to form. 12 A. Yes. 13 BY MR. SLATER: 14 Q. Number 5, you say, "As with 15 other management responsibilities, executive 16 teams must be kept aware of the performance 17 of the quality system and of any emerging 18 problems that are being dealt with." 19 MR. FOX: Is that a question? 20 BY MR. SLATER: 21 Q. That's another important point 22 that you felt needed to be communicated to 23 executive management in pharmaceutical 24 companies, correct?</p>
<p style="text-align: right;">Page 243</p> <p>1 planning and other areas." 2 And then number 3, you say, 3 "Executive management teams must support 4 their QA organization with authority and 5 resources that are equal to the 6 responsibility they have." 7 And then you say a little 8 further down that the structures within the 9 company "must assure that the quality unit 10 can make decisions without undue influence 11 from other organizational components and 12 avoid conflict of interest." 13 Again, these are all what you 14 believe to be very important points for any 15 responsible company to follow, correct? 16 A. Yes, that's correct. 17 Q. Number 4, you wrote, "Executive 18 management must establish a strong quality 19 policy that makes it clear the company is 20 committed to consistently producing 21 high-quality products that perform clinically 22 as intended. Day-to-day statements and 23 actions of top level executives must 24 demonstrate that this commitment is real, not</p>	<p style="text-align: right;">Page 245</p> <p>1 A. Yes. 2 Q. And I think overall what I'm 3 hearing here is that the top level management 4 has to essentially make very clear to 5 everyone in the company that quality is very 6 important, safety is very important, and it 7 should never be minimized and never be put 8 aside for considerations of profit, correct? 9 MR. FOX: Objection to form. 10 A. Yes, correct. 11 BY MR. SLATER: 12 Q. Did you read in the FDA 13 documents where Jung Du told the FDA 14 investigator that the zinc chloride process 15 allowed them to increase their yield and 16 lower their cost, and to thus dominate the 17 world market for valsartan? 18 Did you see that statement? 19 A. Yes, I did. 20 Q. That's a concerning statement 21 to you, isn't it? 22 MR. FOX: Objection to form. 23 Calls for speculation. 24 A. Well, it's a statement that's</p>

Page 246

1 not unreasonable to make if there are
2 benefits to -- you know, enhancing the
3 process for those reasons, that's fine, as
4 long as these other principles we've been
5 discussing are given proper consideration.
6 There's nothing wrong with improving a
7 process, there's nothing wrong with being
8 profitable for that matter, provided that
9 these other principles are respected.
10 BY MR. SLATER:
11 Q. With regard to the e-mail I
12 showed you from July of 2017, matched up
13 against what Jung Du told the FDA
14 investigator, does that cause you some
15 concern about whether or not ZHP kept secret
16 its knowledge that there was NDMA in their
17 valsartan because they were making so much
18 money?
19 MR. FOX: Objection. Calls for
20 speculation.
21 A. I don't see any connection on
22 the surface of it. I think that e-mail by
23 itself certainly is the type of upward
24 communication that I'm talking about here

Page 247

1 that should be made on a regular basis. But
2 there are many questions about what was then
3 done about it, how complete and accurate its
4 foundation was and all that.
5 But that's exactly the sort of
6 thing that should be -- questions that should
7 be asked when someone like Dr. Lin raises
8 that kind of an issue to upper management.
9 BY MR. SLATER:
10 Q. If a decision was made not to
11 investigate in any detail this issue and not
12 to disclose it in any reports or to anybody
13 because of the profits that were being made
14 with this valsartan API, that would be a
15 very, very serious problem, right?
16 MR. FOX: Objection to form.
17 Calls for speculation, argumentative.
18 A. I've certainly seen no evidence
19 that that was the case. But if it was the
20 case, then yes, it would be of concern.
21 BY MR. SLATER:
22 Q. Going now to the Summary at
23 the -- one second actually.
24 Looking at the next section, it

Page 248

1 says, "Common Mistakes Executive Teams Make,"
2 number 3 you wrote, "Emphasizing production
3 quotas and market demands to the extent that
4 quality problems are overlooked or regarded
5 as unimportant - worst case, deliberate
6 coverup of known quality problems through
7 falsification of records." I'm going to stop
8 there.
9 When you say, "worst case,
10 deliberate coverup of known quality problems
11 through falsification of records," you're
12 saying that would be as bad as it gets pretty
13 much, right?
14 A. Yes.
15 Q. Are you aware that -- well,
16 rephrase.
17 To the extent that ZHP knew
18 there was NDMA in its valsartan as of July
19 2017 or earlier, yet continued to represent
20 to customers and regulators and the world
21 that what they were selling was valsartan of
22 the expected quality and the expected purity
23 and didn't disclose the NDMA deliberately,
24 that would be as bad as it gets, right?

Page 249

1 MR. FOX: Objection to form.
2 BY MR. SLATER:
3 Q. If that happened, that's as bad
4 as it gets, right?
5 MR. FOX: Objection to form.
6 Lacks foundation, calls for
7 speculation.
8 A. I don't see enough in the
9 July 2017 e-mail to enable me to conclude
10 with finality that the premise of your
11 question is accurate.
12 There certainly are some
13 concerns expressed there that are appropriate
14 to express, they're being expressed to the
15 right people. But full background and all
16 the facts would have to be delved into with
17 considerable effort in order to reach a
18 conclusion that would have that much impact.
19 BY MR. SLATER:
20 Q. If the conclusion that I
21 postulated were the facts, you would agree
22 that that would be about as bad as it gets,
23 right?
24 MR. FOX: Objection to the

Page 250

1 form. Calls for -- it's
2 argumentative.
3 A. Once again, if after a complete
4 investigation considered all the facts, if it
5 was established and proven based on objective
6 evidence that information existed that was
7 known was deliberately covered up or anything
8 was falsified, then that would be a very
9 serious violation, yes.
10 BY MR. SLATER:
11 Q. Looking now at the Summary, you
12 talked about the fact that there is a
13 "growing consensus about the most critical
14 quality management concepts." And you say,
15 "First among those is that executive
16 management teams are the key to a company's
17 ability to successfully meet quality
18 standards on a consistent basis. Doing so is
19 critical to proper clinical performance of
20 the products of this industry and therefore,
21 ultimately, to global public health."
22 And you would apply those --
23 that point to ZHP? Those points would apply
24 to ZHP, right?

Page 251

1 A. I'm sorry, Adam, can you just
2 have that repeated? It got garbled.
3 Q. This would apply to ZHP,
4 correct?
5 MR. FOX: I'll object to the
6 form because I didn't hear it.
7 BY MR. SLATER:
8 Q. I read the -- I'll do it again.
9 You say in the Summary that
10 certain -- rephrase.
11 You say in the Summary that
12 there's a "growing consensus about the most
13 critical quality management concepts. First
14 among those is that executive management
15 teams are the key to a company's ability to
16 successfully meet quality standards on a
17 consistent basis. Doing so is critical to
18 proper clinical performance of the products
19 of this industry and therefore, ultimately,
20 to global public health."
21 And you would agree that within
22 ZHP, the ultimate responsibility lies with
23 the executive management team, correct?
24 MR. FOX: Objection to form.

Page 252

1 A. Yes, I would agree it applies
2 to ZHP and everybody else in the industry.
3 BY MR. SLATER:
4 Q. Let's go to the last page,
5 please. It's there already, sorry.
6 The last paragraph of this
7 article says, "Prudent management teams
8 recognize this and support their quality
9 units both philosophically and materially,
10 with strong policies backed up by consistent
11 actions, authority and resources. Failure to
12 do so may have both serious business
13 consequences for the company and potentially
14 even personal consequences for individual
15 executives."
16 Again, that's a statement that
17 you believe would hold true for ZHP and any
18 company in this industry, right?
19 A. Yes, any company in this
20 industry.
21 Q. Going back to the events of
22 2017, if ZHP knew that there was NDMA in its
23 valsartan as of at least July 2017, yet
24 continued to manufacture that valsartan with

Page 253

1 the zinc chloride process, didn't change
2 anything, didn't tell anybody, every pill
3 manufactured with that process would be
4 adulterated, right?
5 MR. FOX: Objection to form.
6 A. I'm sorry, I'm giving some
7 thought to the way you phrased that, not the
8 concept, but just the phraseology.
9 If there was proven evidence
10 that the process was contributing NDMA at
11 harmful levels, and they allowed that to
12 continue and continued to sell the product,
13 and particularly if there was any deliberate
14 effort to conceal that, then yes, that would
15 be very serious.
16 MR. SLATER: If you guys need a
17 break, this would be a good point
18 because I'm going to shift to
19 something else. But if you don't need
20 a break, I can do it.
21 MR. FOX: Let's take a break,
22 Adam, because I have to take care of
23 something else for a few minutes, too.
24 A. I need a couple minutes.

Page 254

1 How much time do you want to
2 take here?
3 MR. FOX: About 3:15?
4 THE WITNESS: Okay. What time
5 is it now?
6 MR. SLATER: That's fine.
7 THE WITNESS: Okay. 3:15 is
8 good.
9 MR. SLATER: Thank you.
10 THE VIDEOGRAPHER: The time is
11 2:54 p.m. We are off the record.
12 (Whereupon, a recess was
13 taken.)
14 THE VIDEOGRAPHER: The time is
15 3:23 p.m. We are back on the record.
16 BY MR. SLATER:
17 Q. Mr. Chesney, have you seen any
18 indication in anything you've seen that ZHP
19 has ever notified the FDA about the contents
20 of the July 2017 e-mail we discussed earlier?
21 MR. FOX: Objection to form.
22 A. The existence of the e-mail
23 itself?
24 ///

Page 255

1 BY MR. SLATER:
2 Q. Well, the contents we've been
3 talking about, including that there was NDMA
4 in valsartan --
5 A. Well, the --
6 Q. -- how it was being created at
7 the quenching of the sodium azide, the sodium
8 nitrite, and that it was a common problem
9 with sartan APIs?
10 MR. FOX: Objection to form.
11 Argumentative, lacks foundation.
12 A. There was extensive back and
13 forth with the FDA. ZHP submitted a
14 tremendous amount of scientific data. FDA
15 asked questions, ZHP responded. I've seen a
16 lot of that. Some of it may have contained
17 information that was foundational to that
18 July of '17 e-mail or may not.
19 But the existence of the e-mail
20 itself, I haven't seen reference. It's just
21 the information that it refers to may have
22 been wrapped up and included in some other
23 discussions that were held with the FDA.
24 ///

Page 256

1 BY MR. SLATER:
2 Q. I understand you're saying
3 maybe it was, but nothing you can recall
4 seeing as you sit here now, right?
5 A. No, and nothing specific about
6 that particular e-mail.
7 Q. Did you see any indication in
8 anything you reviewed where ZHP suggested to
9 the FDA or anybody else that it was known
10 internally that there was NDMA in valsartan,
11 and that this was caused by the quenching of
12 the sodium azide with the sodium nitrite,
13 that that was known before June of 2018?
14 Have you seen anything indicating they ever
15 told that to anybody?
16 MR. FOX: Objection to form.
17 Lacks foundation, argumentative.
18 A. Again, I would have to look at
19 the correspondence back and forth to refresh
20 my memory as to what happened when and what
21 they told the FDA about the timeline. But as
22 I sit here, I can't recall anything.
23 BY MR. SLATER:
24 Q. I'm going to jump through a

Page 257

1 couple of things with you.
2 One of the things I noticed in
3 your report was that you said that the time
4 period that you focused on was August 2013 to
5 October 2019, other than, I think, one
6 complaint from 2010 that you found on the FDA
7 website.
8 Do I understand that correctly?
9 A. Not exactly. That wasn't a
10 complaint on the FDA website. It was a
11 record of a prior inspection. And there
12 was -- you know, that was not within that
13 bracketed time period.
14 But the majority of the
15 documents I reviewed were within that
16 bracketed time period.
17 Q. Do you have any
18 understanding -- rephrase.
19 Why would the time period you
20 were looking at beginning 2013 when the
21 manufacturing process change was vetted and
22 evaluated in 2011?
23 A. Well, the primary remit I was
24 given was to opine on what the record showed

<p style="text-align: right;">Page 262</p> <p>1 things at the FDA. In fact, they're still 2 dealing with the backlog caused by that, so 3 that may have been one contributing factor. 4 You know, that whole process of 5 bringing the warning letter to the fore, 6 issuing that, taking the import alert action 7 and clearing all those things up, those 8 things happen very slowly in normal times, 9 and with the intervention of the pandemic, 10 I'm sure it slowed it even further. 11 BY MR. SLATER: 12 Q. Aside from the timing of how 13 long it took, the fact of the matter is that 14 the FDA found some violations, and then ZHP 15 had to take steps to remedy those situations 16 before it could get a closeout letter and get 17 off the import alert, correct? 18 A. With respect to the warning 19 letter, the FDA's formal position is that 20 that's an advisory action, not a final agency 21 determination of noncompliance. 22 And what they characterized 23 those items in the warning letter as 24 internally is observations of regulatory</p>	<p style="text-align: right;">Page 264</p> <p>1 take that very seriously and you make it 2 clear to those companies to take them very 3 seriously, right? 4 A. Without question, yes. 5 Q. I mean, a warning letter is not 6 something that happens every day, and it's a 7 big event in a company's lifecycle that they 8 have to really focus on and deal with very, 9 very seriously, right? 10 A. A warning letter is not 11 something that happens every day to a 12 company, but it's something that happens 13 every day at the FDA. They're not uncommon 14 events. 15 Q. I guess really, I think we've 16 talked about through, but I got the sense 17 that maybe there was a suggestion that a 18 warning letter, because it's not a binding 19 legal action, that it somehow has some kind 20 of minimal significance. That's not what 21 you're saying? 22 A. Oh, no, not at all. I'm sorry 23 if I conveyed that impression. That was not 24 what I intended.</p>
<p style="text-align: right;">Page 263</p> <p>1 significance. They don't term them to be 2 violations because they've not truly been 3 adjudicated at that point in time. 4 Q. I did some reading, and my 5 understanding is that the warning letter is 6 actually a very serious document because the 7 assumption is it's going to get the attention 8 of the company and get the company to fix the 9 situation so that the FDA doesn't have to 10 escalate to direct legal action in court. 11 A. That's correct. I didn't say 12 it wasn't a serious event. It is a serious 13 event. It's just that the agency's official 14 position is that it is an advisory 15 notification intended to stimulate, bring 16 about voluntary corrective action, and also 17 to serve as prior notice in the event they do 18 have to escalate, then they can make showing 19 that they gave the company the opportunity to 20 correct things voluntarily. 21 Q. For the companies, for example, 22 that you consult on -- rephrase. 23 For the companies you consult 24 with, when they get a warning letter, you</p>	<p style="text-align: right;">Page 265</p> <p>1 Q. We're going to digress into 2 something really random right now, which is 3 to clear something up actually. 4 MR. SLATER: Chris, do you have 5 the Exhibit B addendum to the reliance 6 list? I just realized I never marked 7 it as an exhibit. The addendum we got 8 the other day. 9 MR. FOX: What is this? 10 MR. SLATER: I'm sorry, what? 11 MR. FOX: Okay. 12 MR. SLATER: I think, Chris, 13 this is Exhibit 12 now, right? 14 MR. GEDDIS: Yes. 15 MR. SLATER: Okay. Just for 16 everybody to know, we had talked about 17 what exhibit numbers there were. The 18 exhibits have been getting marked 19 sequentially in the deposition. Even 20 though a lot of them had numbers from 21 prior depositions, we've marked them 22 for purposes of this deposition as 23 well so that we know which ones were 24 actually used here, so they're marked</p>

Page 266	Page 268
<p>1 specific to this deposition as well. 2 So this is Exhibit 12. 3 (Whereupon, Chesney Exhibit 4 Number 12 was marked for 5 identification.) 6 BY MR. SLATER: 7 Q. Mr. Chesney, we were provided 8 this the other day, a list of additional 9 references as an addendum to Exhibit B. 10 Are these materials that you 11 have read? 12 A. Not in their entirety. At the 13 onset of this engagement I accessed a number 14 of things that were publicly available just 15 to get some context and bring myself a little 16 bit more up to speed on what was going on 17 with the nitrosamine issue. 18 So these are things that I've 19 pulled from various sources, took a look at, 20 took what I could get from them, more for 21 orientation and contextual purposes and not 22 for specific reliance during the formation of 23 the opinion I submitted in this matter. 24 Q. Were these materials that you</p>	<p>1 would apply, and I think also you said you 2 would do this in a multidisciplinary way 3 where you would rely on subject matter 4 experts with regard to the scientific 5 questions to give input that you could then 6 rely on to give an ultimate opinion. 7 I don't mean to oversimplify, 8 so if you want to tell me a little more you 9 can, but that was generally my understanding 10 of your methodology for evaluating GMP 11 compliance status. 12 A. Well, let me expand that 13 thought a little bit, if you may. 14 If I'm doing this for a client 15 in the sense of either an audit or any other 16 type of consultative activity, then my 17 approach would be more or less the way you 18 mentioned, looking at standard operating 19 procedures perhaps, looking at the actual 20 facility, watching operations, looking at 21 investigations they've done, and things of 22 that sort. 23 For this engagement what I was 24 provided was a lot of FDA documentation,</p>
Page 267	Page 269
<p>1 had available -- rephrase. 2 Are these materials that you 3 had at least looked at before you signed your 4 report -- 5 A. Yes. 6 Q. -- or things you looked at 7 after? 8 A. Yes. I looked at them, most of 9 them, at the very beginning of this 10 engagement back, whatever it was, in June of 11 2021 when I first started doing the work, 12 just to get a sense of the issues and what 13 some of the guidance documents were that FDA 14 and others have come out with on this topic. 15 Q. Okay. In terms of the 16 methodology that you followed here -- well, 17 rephrase. 18 In terms of your normal 19 methodology, if I understood before, normally 20 what you would do when you're evaluating the 21 GMP compliance status for a particular 22 manufacturer would be to evaluate the 23 relevant documents that are available, the 24 internal standard operating procedures that</p>	<p>1 communication from the company and so on. 2 So the way I approached it was 3 first to try to get myself a little bit of a 4 briefing on the general issues. I had read, 5 as I mentioned before, about the NDMA issues, 6 I thought it would help if I understood a 7 little more depth about what was going on 8 here, so I accessed some of these documents 9 for that purpose. It was just for 10 orientation. 11 Then when I got into the 12 documents themselves, I looked at them 13 through the same eyes I would have looked at 14 when I was reviewing identical kinds of 15 documents at the FDA, which I did for many, 16 many years. And I relied to a large extent 17 on FDA's published methodology for doing the 18 same thing, which appears for the most part 19 in their compliance program guidance manual 20 which gives -- all of those programs in part 21 Roman Numeral V, gives instructions to 22 reviewers for what kinds of observations 23 should be considered significant and what 24 regulatory pathways are appropriate in</p>

Page 270

1 different fact situations.
2 So I apply the FDA's own
3 published methodology to determine whether
4 the establishment inspection reports were
5 appropriately classified by the agency based
6 on their own criteria.
7 I also read the establishment
8 inspection reports to determine if the
9 investigators followed the compliance program
10 requirements, collected the correct
11 information, whether their statements are
12 objective or conclusionary, whether they're
13 substantiated with appended evidence. I have
14 a number of factors that I apply that are
15 really the same that I applied when I was
16 reviewing those reports for many years in the
17 FDA.
18 Q. So ultimately, if I understand
19 correctly, when you were evaluating the GMP
20 compliance status, you were doing it through
21 the prism of the back and forth with the FDA
22 and the FDA documents for the most part?
23 A. Largely, yes.
24 Q. And I think that with regard to

Page 271

1 the -- rephrase.
2 We've talked quite a bit about
3 this, so I'm not going to go back into it in
4 any detail, but with regard to scientific
5 issues, that's an area where you've told us
6 you would defer. And since you don't have
7 that at this point you didn't offer opinions
8 in your report as to whether or not there
9 were GMP violations because you would need
10 that input before you could form that
11 opinion, correct?
12 A. Yes, that's correct. And
13 furthermore, the law firm I started working
14 with on this matter, we discussed that angle,
15 and I told him what my limitations were.
16 When we entered into my retention in this
17 matter, I told him there were certain
18 scientific issues that were going to come up
19 that I would not be the best expert to
20 address.
21 And they understood that, said
22 that they had other people that they were
23 working with that could provide that
24 perspective, and not for me to be concerned

Page 272

1 about that, but just to indicate in my report
2 any areas where I was, in fact, deferring to
3 others. And I attempted to do that as I
4 wrote the report. I think you've seen that.
5 Q. Got it.
6 A. Some other documents I relied
7 upon that are referenced in part in the
8 report include the FDA regulatory procedures
9 manual, and certain other publicly available
10 guidance documents that the agency has out
11 there.
12 Q. And at this point we've also
13 talked about some documents and some
14 information you hadn't seen yet. Ultimately
15 if you were to form an opinion, you would
16 want to be able to be assured that you had
17 the relevant documents in doing so, right?
18 A. Well, yes. But I believed I
19 had sufficient information there to make
20 general conclusions and form an opinion as to
21 what the overall compliance status of the
22 facility was.
23 Q. The overall compliance status
24 as we talked about from 2013 to 2019,

Page 273

1 correct?
2 A. That was the major focus, yes,
3 with some excursion back to as early as 2010.
4 Q. That excursion was to one
5 investigation, or one inspection?
6 A. Yes, that's right. I think
7 there was also -- well, no, I guess that
8 would be within the time frame that I
9 bracketed.
10 I think there was another
11 inspection that -- in one of the
12 establishment inspection reports, the FDA
13 person made a statement that the prior
14 inspection was of a certain date, and when I
15 looked at the record, the public record on
16 the FDA data dashboard, there was an
17 inspection that they weren't aware of that
18 they omitted from their text.
19 So there were a few little gaps
20 like that.
21 Q. And overall, for you to be able
22 to form an opinion as to whether GMP was met
23 or not, if you were to do your full-blown
24 methodology, you would want to -- you would

Page 274

1 need to have the full relevant documents.
2 And as you've seen today, you didn't
3 necessarily have all those, the necessary
4 testimony to be able to understand what would
5 actually happen, you would need all that in
6 order to form such an opinion, correct?
7 MR. FOX: Object to the form.
8 A. If there are material
9 omissions, or if there were material
10 omissions in what I was given to review, I
11 was certainly unaware of that at the time.
12 And, you know, of course, if
13 things like that come to light, I become
14 aware of them, it's something I would want to
15 see.
16 BY MR. SLATER:
17 Q. And you would need to see to be
18 able to form an opinion ultimately if it
19 exists, right?
20 MR. FOX: Objection to form.
21 A. Yes. But I don't generally
22 speculate that there's something that is not
23 being provided to me. Unless I'm trying to
24 reach a conclusion and don't have adequate

Page 275

1 information, I would not presume to ask a
2 question such as, Is there anything you're
3 deliberately withholding from me for any
4 reason, because I wouldn't assume that to be
5 the case.
6 BY MR. SLATER:
7 Q. You assumed you were provided
8 all of the relevant documents, correct?
9 MR. FOX: Objection to form.
10 A. I did. And that assumption was
11 bolstered to some extent by my comfort that I
12 had quite a bit of information from which to
13 draw an appropriate conclusion.
14 MR. SLATER: Why don't we go
15 off the record for five minutes. I
16 may be done, I just want to
17 double-check my notes and then we
18 can -- then I can hand it off to
19 Mr. Fox if he has questions too.
20 THE VIDEOGRAPHER: The time is
21 3:44 p.m. We are off the record.
22 (Whereupon, a recess was
23 taken.)
24 THE VIDEOGRAPHER: The time is

Page 276

1 3:47 p.m. We are back on the record.
2 MR. SLATER: Mr. Chesney, thank
3 you. I don't have any other questions
4 for you, unless counsel questions you,
5 in which case I may follow up on his
6 questioning.
7 MR. FOX: I have a few
8 questions, Mr. Chesney.
9 EXAMINATION
10 BY MR. FOX:
11 Q. Do you recall that counsel
12 showed you an e-mail from July 27, 2017,
13 ZHP 296?
14 A. Yes.
15 Q. And does that e-mail involve
16 scientific information of the type that
17 you're not an expert to decipher?
18 A. Yes.
19 MR. SLATER: Objection.
20 You can answer.
21 BY MR. FOX:
22 Q. I'm sorry, did you answer?
23 A. Yes, it does.
24 Q. Now, according to --

Page 277

1 plaintiffs' counsel indicated that there had
2 been testimony taken on that document. Are
3 you aware that there will be additional
4 testimony about that document?
5 MR. SLATER: Objection.
6 You can answer.
7 A. No, I wasn't aware of that.
8 BY MR. FOX:
9 Q. Have you spoken to the author
10 of that document?
11 A. No, I have not.
12 Q. From the substance of the
13 document that was shown to you and that you
14 read, can you determine definitively what was
15 going on in that document?
16 MR. SLATER: Objection.
17 You can answer.
18 A. No. As I said when Mr. Slater
19 asked the question earlier, there are some
20 issues there that are being brought to the
21 attention of upper management, and that
22 seemed to me an appropriate thing to do. But
23 I cannot independently judge fully the
24 significance of the issues.

Page 278

1 BY MR. FOX:
2 Q. Based on your review, did that
3 document indicate that NDMA was in valsartan
4 API?
5 A. It alludes to that at one
6 point. But there's -- you know, again, I
7 can't determine how reliable that statement
8 is or how well substantiated it is. Those
9 are the kinds of questions the leadership
10 team should be asking, and others. Once they
11 get that notification, they should ask for a
12 more complete briefing.
13 Q. Is it your normal practice to
14 opine on company documents?
15 A. I'm sorry, Mr. Fox?
16 Q. Is it your normal practice to
17 offer opinions on company documents?
18 A. Yes, some. If a client asks me
19 to and it's within my expertise, yes.
20 Q. Okay. Was the document dated
21 July 27, 2017 within your expertise?
22 A. No.
23 MR. SLATER: Objection.
24 You can answer.

Page 279

1 BY MR. FOX:
2 Q. You were asked questions
3 earlier by plaintiffs' counsel about unknown
4 peaks, correct?
5 A. Yes.
6 Q. Do you remember that testimony?
7 A. I remember the topic, yes.
8 Q. And did that topic come up in
9 connection with an FDA inspection in May 15th
10 to May 19th of 2017 --
11 MR. SLATER: Objection.
12 BY MR. FOX:
13 Q. -- at the Chuannan plant?
14 MR. SLATER: Objection. Lack
15 of foundation.
16 A. I would have to either look at
17 the inspection report or my report to see if
18 there's any mention of that. My recollection
19 is not precise on that.
20 BY MR. FOX:
21 Q. Okay. I'm going to ask you to
22 turn to page 35 of your report.
23 A. Okay. Got it.
24 MR. SLATER: I'm sorry, what

Page 280

1 page did you say in the report?
2 MR. FOX: 35.
3 MR. SLATER: Give me one
4 second. Okay.
5 BY MR. FOX:
6 Q. Do you see at the bottom of the
7 paragraph it discusses an analysis of peaks?
8 A. Sorry, the bottom of the third
9 paragraph, or...
10 Q. The bottom -- at the bottom of
11 the page, the last six lines of the page.
12 A. Bottom of the page.
13 Yes, uh-huh, I have that.
14 Q. So is the issue of peaks a part
15 of that inspection?
16 A. Apparently was, yes.
17 Q. And did ZHP respond to the
18 issue raised with regard to the peaks?
19 A. Yes, they did.
20 Q. How did they respond to it?
21 A. Well, in at least one instance
22 they said -- they characterized it as a,
23 quote-unquote, "ghost peak with no product
24 quality impact."

Page 281

1 Q. Do you understand why they
2 referred to it as a ghost peak?
3 A. I have a general understanding.
4 Again, I'm not an analytical chemist, I don't
5 do these tests myself, but I have heard that
6 reference made many, many times by
7 pharmaceutical analysts, including those that
8 were in my line of command at the FDA. So I
9 have a general understanding of what it
10 means.
11 Q. And you reported -- you stated
12 in here that there was a report that in the
13 entire year of 2016, there were nine
14 occurrences out of nearly 95,000 batches.
15 Do you see that?
16 A. Yes.
17 Q. In looking at peaks, is the
18 first step to analyze whether they're real or
19 not?
20 A. Yes, usually it is.
21 Q. And is it a possibility that
22 there could be aberrations in the test
23 results?
24 MR. SLATER: Objection.

Page 282

1 You can answer.
2 A. It certainly is. That can come
3 from a number of different sources, including
4 dirty glassware, contaminated solutions,
5 laboratory error. There a whole host of
6 possible ways that these kinds of ghost peaks
7 can appear, and that needs to be investigated
8 and resolved as one of the possible sources.
9 BY MR. FOX:
10 Q. Did the FDA accept that nine
11 occurrences out of nearly 95,000 batches was
12 an aberration?
13 MR. SLATER: Objection.
14 You can answer.
15 A. I don't know what the FDA's
16 opinion about that was.
17 BY MR. FOX:
18 Q. Well, does your report indicate
19 that the FDA's action was consistent with the
20 view that the agency accepted the scientific
21 rationale offered by ZHP?
22 MR. SLATER: Objection.
23 You can answer.
24 A. Let me look and see what --

Page 283

1 just let me back up for a moment here,
2 Mr. Fox.
3 Yes, this -- the classification
4 of this inspection reflects that the FDA
5 would have deemed the compliance status of
6 the facility minimally acceptable. That's
7 their official term for that. That generally
8 means there are a few observations, they are
9 minor and not of regulatory significance.
10 So yes, that's a fair
11 conclusion that they concurred that this did
12 not indicate anything serious.
13 BY MR. FOX:
14 Q. And did it indicate, in your
15 opinion, that the facility at that time was
16 operating in compliance with GMP?
17 MR. SLATER: Objection.
18 You can answer.
19 A. Well, I base my opinion on more
20 than just this, but certainly this didn't
21 cause me to hold an opinion that they were
22 not in compliance with GMP.
23 BY MR. FOX:
24 Q. I believe your testimony is

Page 284

1 that you don't have the scientific background
2 to make an independent judgment with regard
3 to the scientific chemistry issues raised,
4 but you're capable of understanding what the
5 FDA's perception of that scientific evidence
6 was?
7 A. Yes. My capabilities are
8 sufficient that if a subject matter expert
9 offers me a technical explanation, I can
10 usually follow most of it.
11 And if I have questions of
12 areas that I don't understand, then I ask
13 further followup questions. Usually we can
14 reach accord to where they can explain it
15 adequately to my satisfaction, and I can
16 understand what they're telling me.
17 So in other words, I have a
18 modicum of understanding of these things, but
19 I am not an independent subject matter
20 expert.
21 Q. The fact that a company
22 experiences ghost peaks that are viewed to be
23 an aberration, can a company still be
24 compliant with GMP?

Page 285

1 MR. SLATER: Objection.
2 You can answer.
3 A. Yes, they can. In fact, in my
4 personal experience, this happens frequently
5 in pharmaceutical testing laboratories.
6 And my last job in the FDA when
7 I was district director for San Francisco, I
8 had a staff of approximately 50 analysts, of
9 whom 10 or 15 were pharmaceutical chemists.
10 And I know that even in the lab that was in
11 my line of command and control, this issue
12 was not infrequent.
13 So the FDA itself runs into
14 ghost peaks, they resolve them ad hoc as they
15 come up.
16 BY MR. FOX:
17 Q. And during your -- counsel's
18 questioning of you, he showed you a couple
19 sentences here and there in a couple of
20 scientific publications, correct?
21 A. Yes.
22 MR. SLATER: Objection.
23 You can answer.
24 ///

<p style="text-align: right;">Page 286</p> <p>1 BY MR. FOX:</p> <p>2 Q. Is it outside of your</p> <p>3 scientific expertise, or lack thereof, to be</p> <p>4 able to make judgments concerning what was</p> <p>5 known in the scientific literature and the</p> <p>6 quality of that knowledge, given the</p> <p>7 sentences that plaintiffs' counsel showed you</p> <p>8 today?</p> <p>9 MR. SLATER: Objection for</p> <p>10 multiple reasons, including it's</p> <p>11 argumentative.</p> <p>12 You can answer.</p> <p>13 A. I can't evaluate the technical</p> <p>14 sufficiency of those articles. There are</p> <p>15 some portions of it that I frankly don't even</p> <p>16 independently understand, although I might</p> <p>17 understand a good deal of it.</p> <p>18 BY MR. FOX:</p> <p>19 Q. Given the fact that you told</p> <p>20 counsel who retained you of your limited</p> <p>21 expertise when it comes to scientific issues,</p> <p>22 does it surprise you that you would not be</p> <p>23 provided all of the scientific data that may</p> <p>24 be involved in this case?</p>	<p style="text-align: right;">Page 288</p> <p>1 assessment.</p> <p>2 A. Yes.</p> <p>3 Q. And that was conducted in</p> <p>4 connection with the change in the</p> <p>5 manufacturing process?</p> <p>6 A. Yes.</p> <p>7 Q. Am I correct that you testified</p> <p>8 that you assumed that nitrosamines was a part</p> <p>9 of that risk assessment in 2011?</p> <p>10 A. I don't think I understood the</p> <p>11 question if I said that. I was -- what I had</p> <p>12 in mind was the risk assessment that was done</p> <p>13 in four stages in 2018 and reported out in</p> <p>14 the response to the warning letter. That's</p> <p>15 really what I thought we were talking about,</p> <p>16 and I may have become a little confused as to</p> <p>17 the timing.</p> <p>18 Q. Okay. So you never -- you</p> <p>19 never made the assumption that nitrosamines</p> <p>20 was part of 2011 risk assessment, did you?</p> <p>21 MR. SLATER: Objection.</p> <p>22 You can answer.</p> <p>23 A. No, I did not.</p> <p>24 ///</p>
<p style="text-align: right;">Page 287</p> <p>1 MR. SLATER: Objection.</p> <p>2 You can answer.</p> <p>3 A. No, it doesn't surprise me,</p> <p>4 because one of the things -- this was one of</p> <p>5 the concerns I expressed is, Please don't</p> <p>6 expect me to be able to opine on the</p> <p>7 scientific questions. When they come up, I</p> <p>8 will have to say that I need to defer to</p> <p>9 people with appropriate expertise, and I was</p> <p>10 informed that those people would be retained</p> <p>11 separately and would take those issues up as</p> <p>12 they arose.</p> <p>13 BY MR. FOX:</p> <p>14 Q. In connection with the e-mail</p> <p>15 of July 27, 2017 that were shown you,</p> <p>16 ZHP 296, would you defer to other people for</p> <p>17 the correct interpretation of that document?</p> <p>18 A. Yes, I would.</p> <p>19 MR. SLATER: Objection.</p> <p>20 You can answer.</p> <p>21 A. Yes, I would.</p> <p>22 BY MR. FOX:</p> <p>23 Q. Earlier in the day plaintiffs'</p> <p>24 counsel asked you about the 2011 risk</p>	<p style="text-align: right;">Page 289</p> <p>1 BY MR. FOX:</p> <p>2 Q. Is there any reason why you</p> <p>3 would not make that assumption with regard to</p> <p>4 the 2011 risk assessment?</p> <p>5 MR. SLATER: Objection.</p> <p>6 You can answer.</p> <p>7 A. The totality of the information</p> <p>8 that I had before me suggested that the</p> <p>9 industry at large was not really aware of</p> <p>10 this problem, nor had they developed robust</p> <p>11 tests to look for it until much later than</p> <p>12 that.</p> <p>13 This appeared in the two public</p> <p>14 communications on that topic from the FDA;</p> <p>15 one I believe in the latter part of 2018, and</p> <p>16 one in January, I think it was, of 2019 where</p> <p>17 they repeatedly stated that there was not an</p> <p>18 awareness of this problem in the industry nor</p> <p>19 by regulators on a worldwide basis.</p> <p>20 So based upon that, I would not</p> <p>21 have assumed that there was knowledge at ZHP</p> <p>22 or anywhere else in 2011.</p> <p>23 Q. So you're aware of statements</p> <p>24 by the FDA that indicated that it was not</p>

Page 290

1 part of GMP to look for nitrosamines in this
2 process in 2018?
3 MR. SLATER: Objection.
4 A. Yes, I'm aware of those
5 statements. And in those statements, the FDA
6 said it really wasn't feasible for them to
7 even look for that or evaluate it during
8 inspections because there wouldn't be any
9 records that they would be able to review
10 that would reflect that type of analysis had
11 taken place.
12 BY MR. FOX:
13 Q. Are you aware of the FDA ever
14 stating that they were still not sure of the
15 root cause of the NDMA impurity in the
16 valsartan API?
17 MR. SLATER: Objection.
18 You can answer.
19 A. There's a statement that's
20 still being worked on, I believe, in the 2019
21 pronouncement. The specifics escape me. I'm
22 not looking at it right at the moment. But
23 they did make a statement to that effect. I
24 believe it was 2019 January statement.

Page 291

1 MR. FOX: Why don't we put up
2 the -- why don't I put up a document
3 here. Can we go off the record for a
4 second until I get the technology
5 down?
6 THE VIDEOGRAPHER: The time is
7 4:02 p.m. We are off the record.
8 (Off the record.)
9 THE VIDEOGRAPHER: The time is
10 4:04 p.m. We are back on the record.
11 (Whereupon, Chesney Exhibit
12 Number Defendant 1, was marked for
13 identification.)
14 BY MR. FOX:
15 Q. Mr. Chesney, I'm showing you a
16 document of an FDA public statement made on
17 January 25, 2019.
18 Do you see that?
19 A. Yes.
20 Q. And this is reference 91 in
21 your report?
22 A. I'm not looking at the
23 reference numbering list, but give me a
24 moment, I will.

Page 292

1 Yes, that's it.
2 Q. And if I bring you down to the
3 last paragraph of this page, and I'll just
4 read it to you, it says, "Today, we want to
5 provide an update on this ongoing
6 investigation and outline the steps we've
7 taken to identify the root causes of the
8 nitrosamine impurities and to prevent a
9 recurrence of this episode in the future."
10 Do you see that sentence?
11 A. I'm sorry, no, I don't. What
12 I'm looking at starts "last summer."
13 Oh, there. Okay. "Today, we
14 want to provide an update." Now I see it,
15 yes.
16 Q. And so this was an update of an
17 earlier statement that the FDA made in August
18 of 2018?
19 A. Yes.
20 Q. And does this indicate to you
21 that they're still identifying -- trying to
22 identify the root causes of the nitrosamine
23 impurities of valsartan?
24 MR. SLATER: Objection.

Page 293

1 A. Yes, it says it "continues to
2 be an exhaustive effort led by a
3 multidisciplinary team," which is the point
4 I've been trying to make here today, that
5 that's typically the way things are done at
6 FDA. So I'm not surprised by that. A number
7 of people in collaboration with global
8 regulators.
9 And they go on to say, "While
10 we're still investigating the root causes of
11 the impurities, our ongoing effort has
12 determined that the impurities may be
13 generated when specific chemicals and
14 reaction conditions are present."
15 So they're saying the
16 investigation is ongoing, they have what
17 sounds like a hypothesis in their sights, but
18 it appears to be not yet concluded.
19 BY MR. FOX:
20 Q. If we go to the next page, do
21 you see where it says in the beginning of the
22 page, "To implement a risk assessment for any
23 genotoxic impurity"?
24 A. I haven't found it yet. Sorry.

Page 294

1 Oh, there, "To implement a risk assessment."
2 All right. I've got it.
3 Q. And doesn't that last sentence
4 of the paragraph indicate that the FDA had
5 now just uncovered the risk of nitrosamine
6 impurities in the manufacturing steps
7 involved in ARBs?
8 MR. SLATER: Objection.
9 You can answer.
10 A. I'm sorry, I was still reading
11 the sentence, Mr. Fox. Could you repeat the
12 question for me?
13 BY MR. FOX:
14 Q. Doesn't the FDA state in
15 January 2019, quote, "Now that we've
16 uncovered the risk of nitrosamine impurities
17 in the manufacturing steps involved in ARBs,
18 we'll incorporate the findings into ongoing
19 policy development"?
20 A. Yes, they say exactly that.
21 Q. It says here -- do you see the
22 sentence where it says, "Tests are selected
23 based on assessments of what impurities may
24 develop as a result of the manufacturing

Page 295

1 process. In other words, it generally needs
2 to be recognized that there's a risk of an
3 impurity occurring as a result of a
4 manufacturing process to know the impurity
5 should be tested for."
6 Do you see that?
7 A. Yes, I do.
8 Q. Can you read the next sentence
9 into the record, "Our investigation"?
10 A. "Our investigation into ZHP's
11 process identified that a change made to the
12 manufacturing process likely led to this
13 impurity, and that the impurity went
14 undetected by global regulators, including
15 the FDA, for a period of time."
16 Q. Can you read the next sentence?
17 A. Yes. Do you want me to read
18 the whole paragraph?
19 Q. Sure, that would be fine.
20 A. "Before we undertook this
21 analysis, neither regulators nor industry
22 fully understood how NDMA or NDEA could form
23 during this particular manufacturing process.
24 This is troubling to us and we know it's

Page 296

1 troubling to the public. This concern is
2 appropriate. Among other steps, we need to
3 take actions that would prevent a similar
4 situation from occurring. We are making
5 important strides at understanding how these
6 impurities occurred, mitigating the risk to
7 patients and learning what steps need to be
8 taken to prevent this from occurring again in
9 the future."
10 Q. Does this indicate -- have
11 implications for when GMP would have been
12 implicated in connection with nitrosamines?
13 MR. SLATER: Objection.
14 You can answer.
15 A. I'm sorry? Was someone going
16 to interject there?
17 MR. SLATER: I just objected to
18 the form. You can answer.
19 THE WITNESS: Okay.
20 Yes, it indicates to me that
21 certainly prior -- or as of the time
22 of this transmittal to the public,
23 there was enough understanding that
24 companies should be pretty well aware.

Page 297

1 Prior to that time, the
2 statement seems to say that there was
3 not general recognition that this was
4 a risk, and that, therefore, GMP would
5 not require testing for something that
6 no one had awareness could constitute
7 a risk.
8 BY MR. FOX:
9 Q. If we go to the next page, can
10 you read the first line of the paragraph
11 beginning "During this time"?
12 A. Sure. "During this time, our
13 scientists have developed and refined novel
14 and sophisticated testing methods
15 specifically designed to detect and quantify
16 the NDMA and NDEA in all ARB medicines."
17 Q. And this is something that
18 occurred between 2018 and 2019?
19 A. Yes, because this was not the
20 case in the earlier 2018 public statement,
21 but here we have it showing us January 25,
22 2019.
23 (Whereupon, Chesney Exhibit
24 Number Defendant 2 was marked for

<p style="text-align: right;">Page 298</p> <p>1 identification.)</p> <p>2 BY MR. FOX:</p> <p>3 Q. I'm showing you now the earlier</p> <p>4 statement of the FDA that was referred to.</p> <p>5 Can you see that? Do I need to lower it?</p> <p>6 A. You're going to need to shrink</p> <p>7 it a little bit, because the panel with all</p> <p>8 our pictures is overlapping.</p> <p>9 There, now I've got it. That's</p> <p>10 fine right there.</p> <p>11 Q. This is the FDA statement of</p> <p>12 August 30, 2018.</p> <p>13 Do you see that?</p> <p>14 A. Yes.</p> <p>15 Q. And this describes the FDA's</p> <p>16 actions after learning about the impurity in</p> <p>17 the valsartan, correct?</p> <p>18 A. Yes.</p> <p>19 Q. If we go to the second page of</p> <p>20 it, maybe the third page, do you see the</p> <p>21 paragraph that says, "Based on information"?</p> <p>22 A. Yes.</p> <p>23 Q. Can you read that into the</p> <p>24 record, please?</p>	<p style="text-align: right;">Page 300</p> <p>1 ingredient. Before we undertook this</p> <p>2 analysis, neither regulators nor industry</p> <p>3 fully understood how NDMA could form during</p> <p>4 this process."</p> <p>5 Q. Let me just stop you there for</p> <p>6 a second.</p> <p>7 A. Okay.</p> <p>8 Q. Is that an important fact in</p> <p>9 connection with judging cGMP with regard to</p> <p>10 nitrosamines?</p> <p>11 MR. SLATER: Objection.</p> <p>12 You can answer.</p> <p>13 A. Yes, it is, because it speaks</p> <p>14 to the feasibility of doing this and the</p> <p>15 general awareness in the industry of it.</p> <p>16 BY MR. FOX:</p> <p>17 Q. Given this extensive -- you</p> <p>18 would say the FDA's investigation was</p> <p>19 extensive, correct?</p> <p>20 MR. SLATER: Objection.</p> <p>21 You can answer.</p> <p>22 A. I've only reviewed the records</p> <p>23 on ZHP, but their track record is pretty</p> <p>24 extensive there. I'm not sure what they did</p>
<p style="text-align: right;">Page 299</p> <p>1 A. The whole paragraph?</p> <p>2 Q. Yes, please.</p> <p>3 A. Sure. "Based on information</p> <p>4 provided regarding ZHP's manufacturing</p> <p>5 processes, we believed (but did not have</p> <p>6 proof) that the impurity resulted from</p> <p>7 changes that ZHP made to the manufacturing</p> <p>8 process for its API. We needed to identify</p> <p>9 the root cause of the problem and evaluate</p> <p>10 ZHP's explanation. After assessing</p> <p>11 information about ZHP's manufacturing</p> <p>12 processes and the changes ZHP made over time,</p> <p>13 we identified how its processes could have</p> <p>14 led to the presence of NDMA in their API."</p> <p>15 Q. Can you continue with the next</p> <p>16 paragraph?</p> <p>17 A. "Specifically, a combination of</p> <p>18 conditions, which include certain chemicals,</p> <p>19 processing conditions and production steps,</p> <p>20 could lead to formation of the NDMA impurity.</p> <p>21 We believe that these risks are introduced</p> <p>22 through a specific sequence of steps in the</p> <p>23 manufacturing process, where certain chemical</p> <p>24 reactions are needed to form the active</p>	<p style="text-align: right;">Page 301</p> <p>1 with the other manufacturers.</p> <p>2 BY MR. FOX:</p> <p>3 Q. Okay. But certainly this</p> <p>4 public statement is reflecting an extensive</p> <p>5 investigation that the FDA undertook of this</p> <p>6 matter?</p> <p>7 A. Yes, it --</p> <p>8 MR. SLATER: Objection. Form.</p> <p>9 A. It infers that. It doesn't</p> <p>10 describe the full scope of the investigation</p> <p>11 with specifics, but it's implicit, yes.</p> <p>12 BY MR. FOX:</p> <p>13 Q. Now, if you continue with the</p> <p>14 paragraph that says "We are still."</p> <p>15 A. "We are still not 100 percent</p> <p>16 sure that this is the root cause of the</p> <p>17 problem. Full understanding will require</p> <p>18 correlation of multiple test results from</p> <p>19 valsartan APIs made by different processes</p> <p>20 with the various process steps used by</p> <p>21 different manufacturers or at different</p> <p>22 times. We need to determine how NDMA can be</p> <p>23 formed and why it is not separated from the</p> <p>24 API during purification."</p>

Page 302

1 Q. Those statements by the FDA, is
 2 that important information for you in
 3 rendering an opinion with regard to
 4 compliance with cGMP by ZHP?
 5 A. Yes, it is.
 6 Q. Can you read the next
 7 paragraph, please?
 8 A. "Once we understand the way or
 9 ways that the NDMA impurity can occur as a
 10 by-product of the manufacturing process, we
 11 will make sure" that these -- "make sure
 12 these conditions are evaluated in API
 13 synthetic processes so that, in the future,
 14 testing for this impurity would be required
 15 if there was a risk of NDMA formation."
 16 Q. And again, is that an important
 17 factor in rendering an opinion with regard to
 18 ZHP's compliance with cGMP with regard to
 19 nitrosamines?
 20 MR. SLATER: Objection.
 21 You can answer.
 22 A. Yes, because it lays out a
 23 two-pronged test to determine if something --
 24 if this is GMP or not. One is, is there a

Page 303

1 risk of NDMA formation; and two, if so, what
 2 is does the testing show.
 3 BY MR. FOX:
 4 Q. Okay. If you go down a little
 5 bit further, do you see the sentence that
 6 begins "We employ"?
 7 A. Yes.
 8 Q. Can you read that into the
 9 record, please?
 10 A. "We employ robust teams of
 11 organic chemists, as part of our newly
 12 established Office of Pharmaceutical Quality,
 13 to review applications and referenced
 14 information to look for steps - and
 15 manufacturing changes - where these risks
 16 could be introduced."
 17 Q. And if you look at the last
 18 sentence on the page, can you read that into
 19 the record?
 20 A. "In other words, it needs to be
 21 recognized that the risk of an impurity can
 22 occur in order to know that it should be
 23 tested for."
 24 Q. Is it fair to say that prior to

Page 304

1 this date, the FDA did not understand there
 2 to be a risk of an impurity in this
 3 manufacturing process?
 4 MR. SLATER: Objection.
 5 You can answer.
 6 A. It is. That's what the agency
 7 states in this public statement.
 8 BY MR. FOX:
 9 Q. Let's see. I lost my place.
 10 Okay. If we go to the next
 11 page here, do you see -- can you read into
 12 the record the sentence beginning with the
 13 word "Because" in this top paragraph?
 14 A. Yes. Do you want me to read
 15 that?
 16 Q. Please.
 17 A. Okay. "Because it was not
 18 anticipated that NDMA would occur at these
 19 levels in the manufacturing of the valsartan
 20 API, manufacturers would not have been
 21 testing for it. They would not have records
 22 that help identify this issue during an
 23 inspection. So this particular risk would
 24 not have been identified on an inspection.

Page 305

1 As we develop a better understanding of the
 2 root cause of NDMA formation, and develop a
 3 way to detect NDMA in valsartan or other
 4 ARBs, we can ensure that appropriate testing
 5 is performed in the future."
 6 Q. Again, is this an important
 7 fact in determining whether or not GMP was
 8 compliant in connection with nitrosamines in
 9 2018?
 10 A. Yes.
 11 MR. SLATER: Objection.
 12 You can answer.
 13 A. Yes.
 14 BY MR. FOX:
 15 Q. And before 2018, correct?
 16 A. Yes.
 17 Q. And is it true that the FDA is
 18 again stating that they're still seeking to
 19 better understand the root cause of the
 20 formation of this impurity? Is that right?
 21 MR. SLATER: Objection.
 22 You can answer.
 23 A. Yes.
 24 ///

Page 306

1 BY MR. FOX:
 2 Q. And it's also saying in August
 3 of 2018 that they need to find better ways to
 4 detect it.
 5 MR. SLATER: Objection.
 6 You can answer.
 7 A. Yes.
 8 BY MR. FOX:
 9 Q. Is it your testimony that the
 10 compliance record of ZHP was in accord with
 11 or even better than much of the industry
 12 during the period that you reviewed?
 13 MR. SLATER: Objection.
 14 You can answer.
 15 A. Yes. But they had many
 16 inspections that led to no observations at
 17 all, and most others, while they might have
 18 had a small number of observations, they were
 19 classified by the agency as voluntary action
 20 indicated, which is a mid-level
 21 classification that does not reflect a
 22 serious state of noncompliance.
 23 BY MR. FOX:
 24 Q. Did the FDA ever determine that

Page 307

1 the nitrosamine or NDMA present in the
 2 valsartan was the result of a violation of
 3 GMP?
 4 MR. SLATER: Objection.
 5 You can answer.
 6 A. I don't -- I've never seen them
 7 make that specific correlation. In the
 8 warning letter they raised certain concerns,
 9 but I don't believe they ever came right out
 10 and made that connection.
 11 BY MR. FOX:
 12 Q. So as far as you understand,
 13 the FDA never made a determination that the
 14 impurity existed in the valsartan as a result
 15 of a failure to comply with GMP?
 16 MR. SLATER: Objection.
 17 You can answer.
 18 A. I never saw anything that
 19 connected those two issues directly.
 20 BY MR. FOX:
 21 Q. Are you aware of any GMP
 22 violation that would render all of the
 23 products of ZHP adulterated?
 24 MR. SLATER: Objection.

Page 308

1 You can answer.
 2 A. Well, hypothetically I suppose
 3 you could use your imagination and come up
 4 with something that would be so global in
 5 scope that it would cause that.
 6 But usually when that is the
 7 case, and all the products at a given
 8 facility come under that kind of cloud, it's
 9 not just because of any one GMP deviation,
 10 it's because there are multiple ones of a
 11 systemic and repeated nature across all of
 12 what FDA calls product classes in that
 13 particular -- profile classes, pardon me, in
 14 that particular facility.
 15 BY MR. FOX:
 16 Q. And you have not seen that in
 17 connection with ZHP here, have you?
 18 A. No.
 19 MR. SLATER: Objection.
 20 You can answer.
 21 A. No, I haven't.
 22 BY MR. FOX:
 23 Q. And did the FDA ever make a
 24 final determination of a GMP violation by

Page 309

1 ZHP?
 2 MR. SLATER: Objection.
 3 You can answer.
 4 A. I believe the import alert that
 5 they were placed on, along with many, many,
 6 many other companies, was primarily
 7 predicated upon GMP issues. But again, there
 8 was no specific linkage to the occurrence of
 9 NDMA.
 10 BY MR. FOX:
 11 Q. So was the alert due to the
 12 potential of an impurity being in the drug?
 13 MR. SLATER: Objection.
 14 You can answer.
 15 A. The alert is very nonspecific.
 16 It gives a general statement with respect to
 17 GMP compliance, I believe it's one sentence,
 18 and then there's a list of dozens and dozens
 19 and dozens of companies that follow that are
 20 on the import alert for that reason. So it's
 21 very hard to tell anything specific from the
 22 import alert.
 23 BY MR. FOX:
 24 Q. And the language that you're

Page 310

1 referring to, that's template language at the
2 top of the document?
3 A. It is.
4 MR. SLATER: Objection.
5 You can answer.
6 A. It is.
7 And I might add that the
8 standard that FDA applies by statute to bring
9 an import alert action is one of an
10 appearance of a violation, not even a
11 preponderance of the evidence, let alone
12 beyond a reasonable doubt. The standard is
13 very, very low.
14 And I'm getting that directly
15 out of the Food, Drug and Cosmetic Act
16 Section 801. If it appears to be in
17 violation, that's sufficient to take an
18 import alert action. It's a very low
19 standard.
20 BY MR. FOX:
21 Q. Did the FDA ever make a finding
22 that the NDMA contamination was due to a cGMP
23 violation?
24 A. I've never seen them connect --

Page 311

1 MR. SLATER: Objection.
2 You can answer.
3 A. I've never seen them connect
4 those two issues directly in anything they've
5 said in writing.
6 BY MR. FOX:
7 Q. With regard to ZHP?
8 A. With regard to ZHP.
9 MR. FOX: I think that's it for
10 me, Adam.
11 MR. SLATER: I'm going to
12 continue now, Mr. Chesney.
13 FURTHER EXAMINATION
14 BY MR. SLATER:
15 Q. Did you read the deviation
16 investigation reports that ZHP created and
17 submitted to the FDA?
18 A. You know, I read an awful lot
19 of information. And to answer your question
20 whether I did or did not look at those, I
21 would have to go back and look at them again
22 just to be sure. But I believe that I did.
23 Q. I didn't see any discussion of
24 them in your report.

Page 312

1 A. I read a lot of their
2 investigation information, particularly what
3 was in the response to the 483 of the 2018
4 inspection which raised most of these issues,
5 and also the warning letter that followed.
6 There was a tremendous amount of highly
7 detailed information. One of those
8 transmittals alone was 230 pages.
9 So to the extent that
10 constituted in whole or in part the deviation
11 investigations, I can't say from memory. It
12 was very extensive.
13 Q. All right. Well, I didn't ask
14 you about all that stuff.
15 I asked you if you saw the
16 deviation investigation reports, and did you
17 talk about them in your report. I don't see
18 any discussion of them at all in your report.
19 Is there something in the report I've
20 overlooked?
21 A. Well, I doubt that there's
22 anything in the report you've overlooked.
23 What I'm saying is what
24 constituted a deviation investigation report

Page 313

1 may well have been the information in the
2 warning letter response and other documents
3 that I reviewed. They also included a number
4 of attachments.
5 Q. Are you just speculating as you
6 go right now?
7 A. No. I'm trying to say that I
8 can't answer your question with definiteness
9 because I don't know what you mean when you
10 say "a deviation investigation," and I'm not
11 sure whether it was included or not included
12 in any of the materials that I did review.
13 MR. SLATER: Okay. Chris,
14 let's go to exhibit -- let's take down
15 whatever this is, if you could, Tom.
16 MR. FOX: Sorry.
17 MR. SLATER: That's okay.
18 Chris, this might take a
19 second, but could you put up
20 Exhibit 204, please, the deviation
21 investigation report prepared July 20,
22 2018? That's 20 -- oh, you know what,
23 you have the -- that's what I want.
24 ///

Page 318

1 [REDACTED]
2 BY MR. SLATER:
3 Q. Now, you were asked some
4 questions about ghost peaks. Do you know
5 what a ghost peak is? Do you know how that's
6 defined?
7 A. I know that they occur
8 frequently. And as I said before, this is
9 not something I do for a living. I've just
10 heard the term used very often to describe
11 unidentified peaks, they're usually not very
12 large in terms of quantity that may arise
13 from any of a number of different factors and
14 require some investigation to resolve.
15 Q. Do you know the difference
16 between a ghost peak and an aberrant peak?
17 A. No.
18 Q. Do you know if all unknown
19 peaks are ghost peaks?
20 A. No, I think when -- you call
21 something a ghost peak when it's not possible
22 to define with specificity what's causing it,
23 and there are a number of different possible
24 contributing factors that requires an

Page 319

1 investigation to try to iron that out.
2 Q. You're guessing at the
3 definition when you just said that, right?
4 You don't know if you're right?
5 A. I'm telling you what my
6 understanding is. If my understanding is
7 incorrect, then so be it. But that term has
8 been used to me for a number of years, and
9 the context has usually been that.
10 Q. I'm not going to go through
11 those FDA statements that counsel had you
12 read, but I want to ask you a question.
13 There was a point where the FDA
14 was explaining why they didn't find the
15 problem with the NDMA in the valsartan on
16 their inspections.
17 Do you remember you were
18 reading that part?
19 A. Yes.
20 Q. You understand we're not suing
21 the FDA here; we're suing ZHP, right?
22 A. Of course.
23 Q. Okay. And if -- rephrase. And
24 if the manufacturer -- rephrase.

Page 320

1 You said in your report that
2 the FDA primarily relies upon drug
3 manufacturers to voluntarily follow the law,
4 right?
5 A. Yes.
6 Q. That's how the system works, is
7 the companies are supposed to follow the
8 regulations and follow their SOPs so that
9 things like this don't happen, right?
10 MR. FOX: Object to the form.
11 Argumentative.
12 A. Yes.
13 MR. SLATER: Chris, let's go,
14 if we could, to the Warning Letter,
15 ZHP 213, the November 29, 2018 Warning
16 Letter. Thank you.
17 (Whereupon, Chesney Exhibit
18 Number 13 was marked for
19 identification.)
20 BY MR. SLATER:
21 Q. You've seen this document,
22 correct?
23 A. I have.
24 Q. And right there on the first

Page 321

1 page in the second sentence it says, "This
2 warning letter summarizes significant
3 deviations from current good manufacturing
4 practice (CGMP) for active pharmaceutical
5 ingredients (API)," right?
6 A. Yes.
7 Q. And then the next paragraph
8 says, "Because your methods, facilities, or
9 controls for manufacturing, processing,
10 packing, or holding do not conform to CGMP,
11 your API are adulterated within the meaning
12 of section 501(a)(2)(B) of the Federal Food,
13 Drug and Cosmetic Act, 21 USC 351(a)(2)(B)," right?
14 right?
15 A. Yes.
16 Q. And then the FDA says that they
17 reviewed the August 26, 2018 response from
18 ZHP to the 483s, and acknowledged receipt of
19 your subsequent correspondence, right?
20 A. That's right.
21 Q. Let's go through number 1 a
22 little bit. "Failure of your quality unit to
23 ensure that quality-related complaints are
24 investigated and resolved." It says,

Page 322

1 "Valsartan API."
2 You've read this paragraph,
3 right?
4 A. I have. And I've also read
5 ZHP's response to all this to get some
6 balance to the situation.
7 Q. Did I ask you about ZHP's
8 response?
9 A. No, you didn't.
10 Q. Okay. By the way, to the
11 extent that ZHP withheld information from the
12 FDA as part of its investigation, that would
13 be unlawful, correct, if that information was
14 material to the investigation?
15 MR. FOX: Objection to the
16 form. Calls for a legal conclusion.
17 A. That's not an area that I get
18 myself into as a rule. Whether there's been
19 a material misrepresentation or not is --
20 that's usually a legal conclusion.
21 BY MR. SLATER:
22 Q. Okay. This says under number
23 1, "Your firm received a complaint from a
24 customer on June 6, 2018, after an unknown

Page 323

1 peak was detected during residual solvents
2 testing for valsartan API manufactured at
3 your facility. The unknown peak was
4 identified as the probable human carcinogen
5 N-nitrosodimethylamine (NDMA). Your
6 investigation (DCE-18001)" -- and I'll tell
7 you for the record that's the deviation
8 investigation report I just showed you. If
9 you need me to show it to you again I'll show
10 you and show you the number matches up.
11 A. No, that's all right. I take
12 your word for it.
13 Q. -- "determined that the
14 presence of NDMA was caused by the
15 convergence of three process-related factors,
16 one factor being the use of the solvent
17 dimethylformamide (DMF). Your investigation
18 concluded that only one valsartan
19 manufacturing process (referred to as the
20 zinc chloride process in your investigation)
21 was impacted by the presence of NDMA.
22 "However, FDA analyses of
23 samples of your API, and finished drug
24 product manufactured with your API,

Page 324

1 identified NDMA in multiple batches
2 manufactured with a different process, namely
3 the trimethylamine process, which did not use
4 the solvent DMF. These data demonstrate that
5 your investigation was inadequate and failed
6 to resolve the control and presence of NDMA
7 in valsartan API distributed to customers."
8 Do you see what I just read?
9 A. Yes.
10 Q. You've told me you didn't
11 evaluate the TEA process, the triethylamine
12 process, and you didn't talk about it in your
13 report at all, right?
14 A. That's correct.
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 not something you addressed at all in your
21 report, right?
22 A. That was something that falls
23 in the area of process chemistry, and I again
24 would defer to people with the appropriate

Page 325

1 expertise to evaluate that.
2 [REDACTED]
3 [REDACTED]
4 [REDACTED]
5 [REDACTED]
6 [REDACTED]
7 MR. FOX: Objection to form.
8 BY MR. SLATER:
9 Q. Wondering if you know that.
10 A. No, I haven't seen that
11 information.
12 Q. Going back to the document now,
13 the warning letter, it says, "Your
14 investigation also failed:", the first bullet
15 point, "To include other factors that may
16 have contributed to the presence of NDMA."
17 Second bullet point, "To assess
18 factors that could put your API at risk for
19 NDMA cross-contamination.
20 And then the third bullet
21 point, "To evaluate the potential for other
22 mutagenic impurities to form in your
23 products."
24 Do you see that?

<p style="text-align: right;">Page 326</p> <p>1 A. Yes, I do.</p> <p>2 Q. Then the next paragraph, "Our</p> <p>3 investigation also noted other examples of</p> <p>4 your firm's inadequate investigation of</p> <p>5 unknown peaks observed in chromatograms."</p> <p>6 Do you see that?</p> <p>7 A. Yes.</p> <p>8 Q. If you go to the next</p> <p>9 paragraph, it says, "Your response states</p> <p>10 that NDMA was difficult to detect. However,</p> <p>11 if you had investigated further, you may have</p> <p>12 found indicators in your residual solvent</p> <p>13 chromatograms alerting you to the presence of</p> <p>14 NDMA. For example, you told our</p> <p>15 investigators you were aware of a peak that</p> <p>16 eluted after the toluene peak in valsartan</p> <p>17 API residual solvent chromatograms where the</p> <p>18 presence of NDMA was expected to elute. At</p> <p>19 the time of testing, you considered this</p> <p>20 unidentified peak to be noise and</p> <p>21 investigated no further."</p> <p>22 And then it goes through the</p> <p>23 API validation batches, and they indicate</p> <p>24 that these "show at least one unidentified</p>	<p style="text-align: right;">Page 328</p> <p>1 FDA termed grave concerns about what was</p> <p>2 going on in ZHP's facilities, right?</p> <p>3 A. That's correct.</p> <p>4 MR. SLATER: Now let's go to</p> <p>5 the page number 4, please, Chris.</p> <p>6 Q. Heading number 2, "Failure to</p> <p>7 evaluate the potential effect that changes in</p> <p>8 the manufacturing process may have on the</p> <p>9 quality of your API."</p> <p>10 That's relating to the risk</p> <p>11 assessment, correct?</p> <p>12 A. Yes.</p> <p>13 Q. It says, "In November 2011 you</p> <p>14 approved a valsartan API process change that</p> <p>15 included the use of the solvent DMF. Your</p> <p>16 intention was to improve the manufacturing</p> <p>17 process, increase product yield, and lower</p> <p>18 production costs. However, you failed to</p> <p>19 adequately assess the potential formation of</p> <p>20 mutagenic impurities when you implemented the</p> <p>21 new process. Specifically, you did not</p> <p>22 consider the potential for mutagenic or other</p> <p>23 toxic impurities to form from DMF degradants,</p> <p>24 including the primary DMF degradant,</p>
<p style="text-align: right;">Page 327</p> <p>1 peak eluting after the toluene peak in the</p> <p>2 area where the presence of NDMA was suspected</p> <p>3 to elute."</p> <p>4 So I read that as a preview to</p> <p>5 this question, which is the FDA didn't</p> <p>6 think -- you would agree with me the FDA</p> <p>7 didn't think that ZHP did a good job in</p> <p>8 evaluating unknown peaks, right?</p> <p>9 MR. FOX: Objection to form.</p> <p>10 A. That's what the warning letter</p> <p>11 alleges, yes.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. And then if you go to the next</p> <p>14 paragraph at the bottom of this page, page 2</p> <p>15 of this warning letter, in the middle of it,</p> <p>16 it says, "FDA has grave concerns about the</p> <p>17 potential presence of mutagenic impurities in</p> <p>18 all intermediates and API manufactured at</p> <p>19 your facility, both because of the data</p> <p>20 indicating the presence of impurities in API</p> <p>21 manufactured by multiple processes, and</p> <p>22 because of the significant inadequacies in</p> <p>23 your investigation."</p> <p>24 So again, there's some what the</p>	<p style="text-align: right;">Page 329</p> <p>1 dimethylamine. According to your ongoing</p> <p>2 investigation, dimethylamine is required for</p> <p>3 the probable human carcinogen NDMA to form</p> <p>4 during the valsartan API manufacturing</p> <p>5 process. NDMA was identified in valsartan</p> <p>6 API manufactured at your facility."</p> <p>7 Do you see what I just read?</p> <p>8 A. Yes.</p> <p>9 Q. The failure to adequately</p> <p>10 assess the potential formation of mutagenic</p> <p>11 impurities when ZHP implemented the new</p> <p>12 process, that would be a cGMP violation,</p> <p>13 correct?</p> <p>14 MR. FOX: Objection to form.</p> <p>15 A. I think you used the word</p> <p>16 "potential." That's not what it says, but...</p> <p>17 BY MR. SLATER:</p> <p>18 Q. It says "potential formation."</p> <p>19 It says, "However, you failed to adequately</p> <p>20 assess the potential formation of mutagenic</p> <p>21 impurities when you implemented the new</p> <p>22 process."</p> <p>23 And my question to you is, the</p> <p>24 failure to adequately assess the potential</p>

<p>Page 330</p> <p>1 formation of the mutagenic impurities, that's 2 a violation of cGMP, right? 3 MR. FOX: Objection to form. 4 BY MR. SLATER: 5 Q. If that's what happened, it's a 6 violation, correct? 7 MR. FOX: Objection to form. 8 A. I'm sorry, I lost you as you 9 were reading. You must have skipped ahead 10 somewhere and I was reading the wrong 11 sentence. 12 Can you direct me where you're 13 reading? 14 BY MR. SLATER: 15 Q. I'm in the first paragraph 16 under number 2, the third line. 17 A. Oh, okay. 18 Q. It says, "However, you failed 19 to adequately assess" -- 20 A. Okay. I'm sorry. I skipped 21 ahead to far. 22 Q. No problem. 23 You see it says, "However, you 24 failed to adequately assess the potential</p> <p>Page 331</p> <p>1 formation of mutagenic impurities when you 2 implemented the new process"? 3 A. Yes. 4 Q. That would be a cGMP violation, 5 right? 6 MR. FOX: Objection to form. 7 THE WITNESS: I'm sorry, what 8 did you say? 9 MR. FOX: I objected to the 10 form. 11 What was the answer? 12 MR. SLATER: You talked over 13 it, that's why I'm asking him. 14 BY MR. SLATER: 15 Q. Is that correct? 16 A. Yes, that's correct. 17 Q. Going now to the second 18 paragraph under section -- the heading 19 section 2, "You also failed to evaluate the 20 need for additional analytical methods to 21 ensure that unanticipated impurities were 22 appropriately detected and controlled in your 23 valsartan API before you approved the process 24 change."</p>	<p>Page 332</p> <p>1 Stopping right there, that's a 2 cGMP violation, correct? 3 MR. FOX: Objection to the 4 form. 5 A. That should be done, yes. 6 BY MR. SLATER: 7 Q. It says further, I'm going to 8 continue to read, "You are responsible for 9 developing and using suitable methods to 10 detect impurities when developing, and making 11 changes to, your manufacturing processes. If 12 new or higher levels of impurities are 13 detected, you should fully evaluate the 14 impurities and take action to ensure the drug 15 is safe for patients." 16 You agree with that statement, 17 that was an obligation of ZHP, right? 18 MR. FOX: Objection to the 19 form. 20 A. I agree that's a correct 21 statement. 22 BY MR. SLATER: 23 Q. Go to the next paragraph. 24 It says, "Your response" -- now</p> <p>Page 333</p> <p>1 they're talking about that response that you 2 were telling me about before, that you got 3 that long response from ZHP and you read it. 4 Remember you told me that? 5 A. Wait. There are two responses. 6 The one they're referring to here is a 7 response to the 483. 8 There's also a response to this 9 warning letter where they take issue with a 10 number of these points, provide additional 11 data, and a considerable level of detail. 12 So this letter by itself makes 13 certain assertions, but it's not the complete 14 story. 15 Q. Looking now at the third 16 paragraph, the FDA says, "Your response 17 states that predicting NDMA formation during 18 the valsartan manufacturing process required 19 an extra dimension over current industry 20 practice, and that your process development 21 study was adequate. We disagree." 22 MR. FOX: Adam, let me object. 23 Where are you, Adam? 24 MR. SLATER: Third paragraph</p>
---	--

Page 334

1 under number 2. I wasn't planning to
2 do any of this, you brought it up, so
3 I'm just going to hammer the nail.
4 BY MR. SLATER:
5 Q. Third paragraph under number 2,
6 I'll go back to it again. "Your response" --
7 rephrase.
8 The third paragraph under
9 number 2 says, "Your response states that
10 predicting NDMA formation during the
11 valsartan manufacturing process required an
12 extra dimension over current industry
13 practice, and that your process development
14 study was adequate. We disagree."
15 Do you see that?
16 A. I do.
17 Q. So the FDA felt that the
18 process development study was inadequate and
19 there was a violation of cGMP, correct?
20 MR. FOX: Objection to form.
21 A. They -- I don't agree with your
22 statement there, and it's inconsistent with
23 their public statements both before and after
24 this warning letter. But that's what they

Page 335

1 say.
2 BY MR. SLATER:
3 Q. Coming back to my question, the
4 FDA disagreed with ZHP that they couldn't
5 have known about the potential formation of
6 the NDMA, right?
7 MR. FOX: Objection to form.
8 A. They disagreed that it required
9 an extra dimension over current industry
10 practice. That's what the reference is to.
11 BY MR. SLATER:
12 Q. The next sentence says, "We
13 remind you that common industry practice may
14 not always be consistent with CGMP
15 requirements and that you are responsible for
16 the quality of drugs you produce."
17 You agree with that statement,
18 right?
19 A. I do.
20 Q. So when ZHP decided to develop
21 this zinc chloride process that had not been
22 used before, they were responsible for the
23 quality of the drugs that would be
24 manufactured with that new process, right?

Page 336

1 MR. FOX: Objection to form.
2 A. Yes, they were responsible.
3 BY MR. SLATER:
4 Q. And the fact that nobody else
5 had been manufacturing by that process
6 previously doesn't change the fact or excuse
7 the fact that they failed to evaluate fully
8 the risks from that new process?
9 MR. FOX: Objection to form.
10 A. The fact that nobody else was
11 using the process does not relieve them of
12 the necessity to evaluate it fully.
13 MR. SLATER: Okay. Let's take
14 that down. Let's go, Chris, if we
15 could, to Exhibit 212.
16 (Whereupon, Chesney Exhibit
17 Number 14 was marked for
18 identification.)
19 BY MR. SLATER:
20 Q. This was previously marked as
21 Exhibit 212 at a deposition of Peng Dong. I
22 assume you haven't seen this. It's a draft
23 of a deviation investigation report.
24 A. From the cover page I couldn't

Page 337

1 tell you.
2 And could you make it a little
3 bit larger? It's a little small on my
4 screen.
5 Q. No problem.
6 A. The cover page I don't
7 recognize, but I don't know.
8 Q. Well, I'm going to represent to
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]
14 [REDACTED]
15 [REDACTED]
16 [REDACTED]
17 [REDACTED]
18 [REDACTED]
19 [REDACTED]
20 [REDACTED]
21 [REDACTED]
22 [REDACTED]
23 [REDACTED]
24 Do you see what I just read?

Page 338

1 A. Yes.

2 Q. And if that's what happened,

3 that was a violation of cGMP, as we've gone

4 through earlier, correct?

5 MR. FOX: Objection to form.

6 A. Again, I can't characterize an

7 individual occurrence like that as a

8 violation or not a violation. That requires

9 a lot more consideration.

10 But it's concerning and

11 certainly worthy of everyone's attention,

12 including those at the company that received

13 this report.

14 MR. SLATER: Take that down.

15 The next thing I'd like to go

16 to, if we could, is -- I believe it

17 was Exhibit 430. It's the August 26,

18 2018 response to the 483 letter.

19 (Whereupon, Chesney Exhibit

20 Number 15 was marked for

21 identification.)

22 MR. SLATER: Signed by Jun Du.

23 MR. GEDDIS: Give me a second.

24 THE VIDEOGRAPHER: Excuse me,

Page 339

1 Attorney Slater?

2 MR. SLATER: Yes.

3 THE VIDEOGRAPHER: May we go

4 off the record for a moment? I have

5 approximately ten minutes left on this

6 backup media recording.

7 MR. SLATER: No, I want to

8 continue. We'll be done in ten

9 minutes. I'm also through.

10 THE VIDEOGRAPHER: Okay, sir.

11 MR. SLATER: Don't worry about

12 it. If I start to run into it and get

13 to two minute, let me know.

14 THE VIDEOGRAPHER: The Zoom is

15 going, just the backup.

16 MR. SLATER: Are we okay?

17 THE VIDEOGRAPHER: The Zoom is

18 recording, yes. The backup media had

19 approximately ten minutes left.

20 MR. SLATER: Okay. Just let me

21 know if we get to two minutes.

22 THE VIDEOGRAPHER: Okay, sir.

23 MR. SLATER: While Chris is

24 looking for that, you might as well --

Page 340

1 okay. He got it.

2 BY MR. SLATER:

3 Q. Okay. This is the August 26,

4 2018 letter from Jun Du of ZHP to the FDA.

5 You've seen this, correct?

6 A. Yes, I have.

7 Q. Let's go to page 3 of 4,

8 please.

9 MR. SLATER: And let's blow up

10 that middle paragraph, if we could,

11 just so we can all see it. Okay.

12 Perfect.

13 [REDACTED]

14 [REDACTED]

15 [REDACTED]

16 [REDACTED]

17 [REDACTED]

18 [REDACTED]

19 [REDACTED]

20 [REDACTED]

21 [REDACTED]

22 [REDACTED]

23 MR. FOX: Objection to the

24 form.

Page 341

1 A. You showed me a document that

2 had a suggestion of that. But as I

3 indicated, it's got some technical aspects

4 that I'm not comfortable evaluating, and

5 would trigger a lot more questions in my mind

6 before I would be prepared to make a

7 definitive statement about it.

8 BY MR. SLATER:

9 Q. The July 2017 e-mail doesn't

10 make any suggestion, it states definitively

11 that there's NDMA in valsartan, the root

12 cause is the quenching of the sodium azide in

13 the presence of sodium nitrite, and says it's

14 a problem with all the sartans, across

15 sartans. That's what it says. It doesn't

16 speculate about it; it makes those factual

17 statements, right?

18 MR. FOX: Objection. Object to

19 the form. Argumentative.

20 A. It presents the information in

21 that way, yes.

22 BY MR. SLATER:

23 Q. All of which you can tell me

24 sitting right now is accurate because we know

Page 342	Page 344
Page 343	Page 345
<p>1 historically that was all proven true, those 2 factual statements, right?</p> <p>3 MR. FOX: Objection to the 4 fact -- objection to the form.</p> <p>5 A. Most of that proved to be 6 correct. But again, putting myself in the 7 position of having received that at that 8 point in time, I would have had a host of 9 more questions.</p> <p>10 BY MR. SLATER:</p> <p>11 Q. It's not some of it has been 12 proven correct, all of those three things 13 have been proven correct, right?</p> <p>14 MR. FOX: Objection to the 15 form. Argumentative.</p> <p>16 A. I, at this point, am not sure 17 specifically what we're talking about in 18 terms of all of them.</p> <p>19 BY MR. SLATER:</p> <p>20 Q. There's NDMA in valsartan, it's 21 caused when they quench the sodium azide with 22 sodium nitrite, and it's a problem with 23 multiple sartans. That's been proven true, 24 right?</p>	<p>1 talking there. I wasn't sure where we were 2 with this.</p> <p>3 Could you restate the question, 4 because I heard multiple people.</p> <p>5 Q. Sure.</p> <p>6 ZHP has always told the FDA it 7 did not learn of what we just talked about 8 until June of 2018 at the earliest, right?</p> <p>9 A. That's when they reached the 10 final conclusion, yes. That's what they told 11 the FDA.</p> <p>12 Q. Well, they claimed that they 13 didn't even know there was NDMA in the 14 valsartan until June of 2018, right?</p> <p>15 MR. FOX: Objection to form.</p> <p>16 A. That they -- they wouldn't have 17 said they knew it until they were sure of it.</p> <p>18 MR. SLATER: Let's take that 19 down and go to Exhibit 312, the 20 establishment inspection report. 21 (Whereupon, Chesney Exhibit 22 Number 16 was marked for 23 identification.) 24 MR. SLATER: Do we have at</p>
<p>1 MR. FOX: Objection to the 2 form.</p> <p>3 A. Yes. At a high level, yes, 4 that's true.</p> <p>5 BY MR. SLATER:</p> <p>6 Q. And just to be clear, Jun Du 7 represented that this wasn't learned until 8 June of 2018. That's what he represented to 9 the FDA, right?</p> <p>10 MR. FOX: Objection to form. 11 Argumentative, document speaks for 12 itself.</p> <p>13 MR. SLATER: All right. Look, 14 I'll ask it again.</p> <p>15 BY MR. SLATER:</p> <p>16 Q. It's a fact that ZHP has always 17 represented to the FDA that those facts 18 weren't learned until June 2018, right?</p> <p>19 MR. FOX: Well, ask the 20 question.</p> <p>21 BY MR. SLATER:</p> <p>22 Q. Can you answer that? That's 23 correct, right?</p> <p>24 A. I'm sorry, I heard two people</p>	<p>1 least another five minutes left on 2 that backup? Okay.</p> <p>3 BY MR. SLATER:</p> <p>4 Q. Here on the screen we have the 5 Establishment Inspection Report, Exhibit 312. 6 Do you see that?</p> <p>7 A. Yes.</p> <p>8 Q. And I just want to go to 9 page 20 of 58. Looking at the paragraph that 10 says, "During the opening presentation." 11 MR. SLATER: Let's blow that up 12 a little bit. Perfect.</p> <p>13 Q. This states, "During the 14 opening presentation on July 23, 2018, Mr. Du 15 explained how the firm came to know Valsartan 16 manufactured by the firm could contain the 17 genotoxic impurity NDMA. Mr. Du stated 18 Novartis placed an order with the firm for 19 45 Metric Tons of valsartan." And then he 20 goes through it and talks about how it was 21 Novartis that told ZHP of this issue, right?</p> <p>22 A. Let me read the paragraph here. 23 (Witness reviewing document.) 24 A. Okay. So okay, I've read the</p>

<p style="text-align: right;">Page 346</p> <p>1 paragraph. Now, what was the question again?</p> <p>2 Q. This is reciting what Jun Du</p> <p>3 told the FDA at the time of the inspection of</p> <p>4 July 23, 2018, right?</p> <p>5 A. Yes.</p> <p>6 Q. Based on the content of the</p> <p>7 e-mail from July of 2017 showing that ZHP</p> <p>8 already knew there was NDMA in the valsartan</p> <p>9 and why it was occurring, when Mr. Du spoke</p> <p>10 to the FDA that day, he lied to the FDA,</p> <p>11 correct?</p> <p>12 MR. FOX: Objection. Calls for</p> <p>13 conclusion, speculation.</p> <p>14 A. I can't conclude that based on</p> <p>15 what I see here.</p> <p>16 BY MR. SLATER:</p> <p>17 Q. What Jun Du told the FDA was</p> <p>18 untrue in comparison to what that July 2017</p> <p>19 e-mail shows, correct?</p> <p>20 MR. FOX: Objection to form.</p> <p>21 Beyond his expert report, calls for a</p> <p>22 legal conclusion.</p> <p>23 A. Again, I am still not confident</p> <p>24 of the state of the firm's awareness,</p>	<p style="text-align: right;">Page 348</p> <p>1 FURTHER EXAMINATION</p> <p>2 BY MR. FOX:</p> <p>3 Q. Mr. Chesney, can something that</p> <p>4 occurred in this instance with impurity found</p> <p>5 in valsartan, could that have occurred even</p> <p>6 though everyone followed the law?</p> <p>7 MR. SLATER: Objection.</p> <p>8 A. Yes.</p> <p>9 BY MR. FOX:</p> <p>10 Q. In regard to GMP and cGMP, what</p> <p>11 does the "C" stand for?</p> <p>12 A. Current.</p> <p>13 Q. Does cGMP change over time?</p> <p>14 A. Yes.</p> <p>15 Q. Did cGMP change with regard to</p> <p>16 nitrosamines in the 2019 time frame as far as</p> <p>17 the FDA is concerned?</p> <p>18 MR. SLATER: Objection.</p> <p>19 A. I would draw that conclusion</p> <p>20 from the public statements that we looked at</p> <p>21 earlier, 2018 and 2019, that as information</p> <p>22 was developed and better understood, the</p> <p>23 expectations rose and were still, in fact,</p> <p>24 rising at the time of the January 25, 2019</p>
<p style="text-align: right;">Page 347</p> <p>1 notwithstanding Dr. Lin's statement in his</p> <p>2 July 17th e-mail. For me to accept that as</p> <p>3 fact, I would need to see considerably more</p> <p>4 backup information that that statement is</p> <p>5 based upon and have it evaluated by</p> <p>6 scientific experts to be sure it's right.</p> <p>7 Because an allegation such as</p> <p>8 that that he was not being truthful is very</p> <p>9 serious and needs to be vetted in</p> <p>10 considerable detail, and I think FDA would</p> <p>11 approach it the same way.</p> <p>12 BY MR. SLATER:</p> <p>13 Q. If ZHP wasn't truthful with the</p> <p>14 FDA as to when they learned there was NDMA in</p> <p>15 the valsartan and how it was occurring, if</p> <p>16 that occurred, that's a very, very serious</p> <p>17 violation, right?</p> <p>18 MR. FOX: Objection. Asked and</p> <p>19 answered.</p> <p>20 A. Yes, that would be a</p> <p>21 significant violation, yes.</p> <p>22 MR. SLATER: I don't have any</p> <p>23 other questions unless your counsel</p> <p>24 wants to ask you more.</p>	<p style="text-align: right;">Page 349</p> <p>1 statement.</p> <p>2 BY MR. FOX:</p> <p>3 Q. And when cGMP changes, does the</p> <p>4 FDA typically apply it retroactively to the</p> <p>5 industry?</p> <p>6 MR. SLATER: Objection.</p> <p>7 You can answer.</p> <p>8 A. No.</p> <p>9 BY MR. FOX:</p> <p>10 Q. That would be unfair, wouldn't</p> <p>11 it?</p> <p>12 MR. SLATER: Objection.</p> <p>13 You can answer.</p> <p>14 A. Yes, it would be unfair, and</p> <p>15 that has not been the practice, to my</p> <p>16 knowledge.</p> <p>17 MR. FOX: No further questions.</p> <p>18 MR. SLATER: I don't have any</p> <p>19 other questions.</p> <p>20 MR. FOX: Thank you,</p> <p>21 Mr. Chesney.</p> <p>22 Thank you, Adam.</p> <p>23 MR. SLATER: Thank you very</p> <p>24 much.</p>

<p style="text-align: right;">Page 350</p> <p>1 THE WITNESS: Thank you, 2 Mr. Slater. 3 MR. SLATER: It was nice to 4 meet you. I hope everybody has a nice 5 evening. 6 THE WITNESS: Thank you. Same 7 to you, sir. 8 THE VIDEOGRAPHER: The time is 9 5:03 p.m. We're off the record. This 10 concludes today's deposition. 11 (Whereupon, the deposition was 12 concluded.) 13 14 15 16 17 18 19 20 21 22 23 24</p>	<p style="text-align: right;">Page 352</p> <p>1 INSTRUCTIONS TO WITNESS 2 3 Please read your deposition over 4 carefully and make any necessary corrections. 5 You should state the reason in the 6 appropriate space on the errata sheet for any 7 corrections that are made. 8 After doing so, please sign the 9 errata sheet and date it. It will be 10 attached to your deposition. 11 It is imperative that you return 12 the original errata sheet to the deposing 13 attorney within thirty (30) days of receipt 14 of the deposition transcript by you. If you 15 fail to do so, the deposition transcript may 16 be deemed to be accurate and may be used in 17 court. 18 19 20 21 22 23 24</p>
<p style="text-align: right;">Page 351</p> <p>1 CERTIFICATE 2 3 I, MAUREEN O'CONNOR 4 POLLARD, Registered Diplomat 5 Reporter, Realtime Systems 6 Administrator, and Certified Shorthand 7 Reporter, do hereby certify that prior 8 to the commencement of the 9 examination, DAVID L. CHESNEY, was 10 remotely duly identified and sworn by 11 me to testify to the truth, the whole 12 truth, and nothing but the truth. 13 I DO FURTHER CERTIFY that 14 the foregoing is a verbatim transcript 15 of the testimony as taken 16 stenographically by and before me at 17 the time, place, and on the date 18 hereinbefore set forth, to the best of 19 my ability. 20 I DO FURTHER CERTIFY that 21 I am neither a relative nor employee 22 nor attorney nor counsel of any of the 23 parties to this action, and that I am 24 neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action. _____ MAUREEN O'CONNOR POLLARD NCRA Registered Diplomat Reporter Realtime Systems Administrator Certified Shorthand Reporter Notary Public Dated: March 24, 2022</p>	<p style="text-align: right;">Page 353</p> <p>1 ----- 2 E R R A T A 3 ----- 4 PAGE LINE CHANGE 5 _____ 6 REASON: _____ 7 _____ 8 REASON: _____ 9 _____ 10 REASON: _____ 11 _____ 12 REASON: _____ 13 _____ 14 REASON: _____ 15 _____ 16 REASON: _____ 17 _____ 18 REASON: _____ 19 _____ 20 REASON: _____ 21 _____ 22 REASON: _____ 23 _____ 24</p>

ACKNOWLEDGMENT OF DEPONENT

I, _____, do
Hereby certify that I have read the foregoing
pages, and that the same is a correct
transcription of the answers given by me to
the questions therein propounded, except for
the corrections or changes in form or
substance, if any, noted in the attached
Errata Sheet.

DAVID L. CHESNEY DATE

Subscribed and sworn
To before me this
_____ day of _____, 20____.

My commission expires: _____

Notary Public

LAWYER'S NOTES

PAGE LINE

1	_____	_____
2	_____	_____
3	_____	_____
4	_____	_____
5	_____	_____
6	_____	_____
7	_____	_____
8	_____	_____
9	_____	_____
10	_____	_____
11	_____	_____
12	_____	_____
13	_____	_____
14	_____	_____
15	_____	_____
16	_____	_____
17	_____	_____
18	_____	_____
19	_____	_____
20	_____	_____
21	_____	_____
22	_____	_____
23	_____	_____
24	_____	_____

Exhibit 14

2006 WL 166452

2006 WL 166452

Only the Westlaw citation is currently available.

NOT FOR PUBLICATION

United States District Court, D. New Jersey.

Jeff PLAYER, et al., Plaintiffs,

v.

MOTIVA ENTERPRISES LLC, a successor
in interest to Star Enterprises, Defendant.

No. Civ. 02-3216(RBK).

|

Jan. 20, 2006.

Attorneys and Law FirmsKeith A. McKenna, McKenna, Mulcahy & McKenna,
Montclair, NJ, for Plaintiffs.Jeffrey W. Moryan, Connell Foley LLP, Roseland, NJ, for
Defendant.**OPINION**

KUGLER, United States District Judge:

*1 This matter comes before the Court upon motions by Defendant Motiva Enterprises, LLC, ("Defendant" or "Motiva") for summary judgment of the claims of Plaintiffs Jeff Player, et al. ("Plaintiffs"), and to exclude Plaintiffs' experts Michael Gochfeld, M.D., Ph.D. ("Gochfeld"), R. Brian Ellwood, Ph.D. ("Ellwood"), Bruce M. Gallo ("Gallo"), and Daniel McDonald ("McDonald"). For the reasons set forth below, Defendant's motions will be granted in part and denied in part.

I. Background¹

This environmental contamination suit is brought by the current and former owners of twenty-seven parcels of residential property located in the Spring Hollow Subdivision in Gloucester Township, New Jersey.² Plaintiffs allege that emissions from Defendant's nearby Texaco gasoline service station contaminated their property and the Kirkwood Cohansey Aquifer, the underground water source for their potable wells.

Contamination of the aquifer was first detected on April 5, 2000, when significant concentrations of the gasoline-related compound methyl tertiary butyl ether ("MTBE") was discovered in a drinking fountain at Camden County Community College. New Jersey Consumers Water Company ("Consumers"), the entity responsible for providing water to the college, conducted sampling of some of its wells and discovered significant amounts of gasoline-related compounds in municipal supply well number 8 ("CW-8"). Consumers took the well offline on April 10.

While investigating the contamination, the New Jersey Department of Environmental Protection ("NJDEP") detected a discharge of volatile organic compounds ("VOCs") from Defendant's service station, located at 585 Berlin Cross Keys Road ("Motiva site" or "contamination site").³ The NJDEP issued a Field Directive on April 12, 2000, requiring Motiva to investigate the source and extent of the discharge, to implement an interim treatment system, and to submit a remedial action work plan to the NJDEP. Defendant installed an interim recovery system and twenty-five monitoring and recovery wells between April and June 2000.

The NJDEP issued a second directive on May 5, 2000, ordering Defendant to cease gasoline retail operations and provide treatment or an alternate source of water to replace CW-8. Defendant replaced the interim system with a permanent ground water recovery and treatment system in June 2000, and installed forty-one additional monitoring wells from June 2000 to present. As further required by the NJDEP, Defendant regularly sampled potable wells located on approximately forty residential properties in the vicinity of the Motiva site. Defendant detected small amounts of MTBE in thirteen of the residential wells it sampled.⁴

Per the NJDEP directive, Motiva submitted a Remedial Investigation Work Plan/Remedial Investigation report on July 2000 and a Remedial Action Workplan ("RAW") on November 14, 2000. In its RAW, Defendant requested permission to cease sampling of the residential wells, contending that the MTBE detected in those wells could not have come from the Motiva site since the wells are located upgradient⁵ or sidegradient from the site, and no emissions were detected in most of the monitoring wells between the Motiva site and the potable wells.⁶ Motiva also claimed that recent literature indicated that traces of MTBE in groundwater could likely result from "non-point sources." (March 2001 Directive at 2.)

2006 WL 166452

*2 Plaintiffs' expert, R. Brian Ellwood, Ph.D ("Ellwood"), submitted a response to the RAW on January 17, 2001. In his report, Ellwood notes that as of January 17, 2001, "[c]ontrol of contamination at depth beneath the site, control of offsite contamination, and possibly control of contamination at the northern site boundary, has not been established." (Preliminary Report Sicklerville Road Groundwater Contamination ("Ellwood Report"), McKenna Cert. in Opp. to Def.'s Mot. Summ. J., filed Oct. 12, 2005 ("McKenna Cert."), Ex. F, at 2.) Ellwood also offered possible theories to demonstrate the plausibility of Defendant's responsibility for the MTBE in spite of Motiva's arguments to the contrary.

The NJDEP ultimately rejected Defendant's request to cease sampling of the residential wells in its March 2001 Directive on the basis that "there is insufficient evidence for Equiva to conclude that the MTBE detected in the 13 potable wells in the area did not originate from the Cross Keys Texaco site" and "that regardless of the source of the MTBE in these wells, which is obviously debatable, ongoing sampling of these wells is required *primarily due to their proximity to the site.*" (March 2001 Directive at 2) (emphasis in original).

Also in the March 2001 Directive, the NJDEP approved a Classification Exemption Area ("CEA") for the site that excluded all but 1/10 of an acre of 583 Berlin Cross Keys Road (the Wallace Property). The CEA establishes the boundaries of a ground water plume where VOCs exceed the GWQS.⁷

Through summer 2004, the NJDEP regularly reduced the testing requirements. By August 18, 2003, the NJDEP required only:

annual sampling of the wells at 4, 7, 11, 13 and 14 Donna Marie Court; 2, 4, 6, and 8 Latham Way; 12 and 20 Spring Hollow Drive, and; 937 and 948 Sicklerville Road. For all the sampling events of the aforementioned potable wells conducted April 2002, the Department notes that all wells continue to exhibit no gasoline related contamination in

excess of the Department's Drinking Water Quality Standards.

(NJDEP Directive, Aug. 18, 2003, McKenna Cert., Ex. D.)

The NJDEP approved shut down of the recovery and treatment system on April 30, 2004. (NJDEP Correspondence, Aug. 9, 2004, Mairo Cert., Ex. S., at 2.) Finally, on August 9, 2004, the NJDEP determined that "Defendant's Remedial Action Progress Reports "meet the conditions of the March 21, 2001 Remedial Action Workplan (RAW) approval. Shell Oil Products U.S. (Shell OPUS) is, therefore, in compliance with N.J.A.C. 7:14B-6." (Aug. 9, 2004, NJDEP Correspondence, Mairo Cert., Ex. S., at 1.)

B. The Residential Properties

Plaintiffs own twenty-seven respective residential properties near Defendant's gasoline station.⁸ Twenty-six of the twenty-seven properties-all but 583 Berlin Cross Keys Road ("the Wallace property")-contain potable wells located in the Kirkwood Cohansey Aquifer. Because Plaintiffs' properties are north/northeast of the contamination site, (Undisputed Facts ¶ 38), they are considered upgradient or sidegradient of the contamination site, depending on whether CW-8 is pumping.⁹

*3 Consistent with the requirements of the NJDEP directives, Defendant tested the Plaintiffs' residential wells for six gasoline-related compounds: benzene, toluene, ethylbenzene, xylenes, MTBE, and TBA. No testing detected any gasoline-related compound on eighteen of the properties.¹⁰ Detection of compounds on the remaining eight properties was as follows:

- A single detection of 0.79 ppb toluene and ten detections of MTBE (highest at 15.5 ppb) at 4 Latham Way,
- Three detections of MTBE (highest at 0.76 ppb) at 14 Donna Marie Court,
- Three detections of MTBE (highest at 1.4 ppb) at 6 Latham Way,
- A single detection of 1.4 ppb toluene at 850 Sicklerville Road,

2006 WL 166452

- A single detection of 0.4 ppb MTBE at 4 Donna Marie Court,
- A single detection of 0.3 ppb MTBE at 12 Donna Marie Court,
- A single detection of 1.2 ppb MTBE at 8 Latham Way, and
- A single detection of 0.3 ppb MTBE at 20 Spring Hollow Road.

The GWQS for toluene is 1,000 ppb and the GWQS for MTBE is 70 ppb. No gasoline-related compound was detected on any Plaintiff's property after April 2001.

According to the Certification of Julian Davies, a Project Manager for EnviroTrac, Ltd., an environmental consulting firm retained by Defendant to remediate the Motiva site, the NJDEP never restricted the consumption of water from Plaintiffs' potable wells, and never required Defendant to treat the water, provide Plaintiffs with an alternate source of water, or collect soil samples from the residential properties.¹¹ (Julian Davies Cert., Mairo Cert., Ex. R, at 2.)

Since the fact of the contamination became known, several Plaintiffs have sold their property. Maria and John Wallace sold 583 Berlin Cross Keys Road for \$350,000.00 in September 2001, Plaintiffs Thomas and Tina Stankiewicz sold 9 Spring Hollow Drive in July 2002 for \$143,000.00, Barbara Tanner sold 17 Spring Hollow Drive for \$134,000.000 in February 2002, Daniel and Maria Rodriguez sold 18 Spring Hollow Drive for \$138,000.00 in July 2003, David Lodi sold 5 Donna Marie Court for \$104,000.00 in September 2001, 13 Donna Marie Court was sold for \$109,900.00 in July 2000, and 19 Spring Hollow Drive was sold for \$133,900.00 in May 2001.

Defendant filed motions for summary judgment and to exclude experts on June 24, 2005, after requesting and receiving permission from this Court to extend by one week the date for the filing of dispositive and *in limine* motions. Briefs in opposition were due July 22, 2005, however, Plaintiffs instead filed an untimely request for an extension on August 2, 2005, and a second request on September 6, 2005, moving the deadline to September 30, 2005. On October 5, 2005, Plaintiffs filed another untimely request for an extension, and ultimately did not submit a complete Opposition until October 14, 2005. Nevertheless, because a district court should not grant a

motion for summary judgment without examining the merits,

Stackhouse v. Mazurkiewicz, 951 F.2d 29, 30 (3d Cir.1991)

(citing *Anchorage Assoc. v. Virgin Islands Bd. of Tax Rev.*, 922 F.2d 168 (3d Cir.1990)), this Court will exercise its discretion to consider Plaintiffs' Opposition, even though it is untimely. Local Civ. R. 7.1(d)(5).

II. Standard

*4 Summary judgment is appropriate where the Court is satisfied that "there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 330, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986). A genuine issue of material fact exists only if "the evidence is such that a reasonable jury could find for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

The burden of establishing the nonexistence of a "genuine issue" is on the party moving for summary judgment.

Celotex, 477 U.S. at 330. The moving party may satisfy this burden by either (1) submitting affirmative evidence that negates an essential element of the nonmoving party's claim; or (2) demonstrating to the Court that the nonmoving party's evidence is insufficient to establish an essential element of the nonmoving party's case. *Id.* at 331.

Once the moving party satisfies this initial burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e). To do so, the nonmoving party must "do more than simply show that there is some metaphysical doubt as to material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986). Rather, to survive summary judgment, the nonmoving party must "make a showing sufficient to establish the existence of [every] element essential to that party's case, and on which that party will bear the burden of proof at trial."

Serbin, 96 F.3d at 69 n. 2 (quoting *Celotex*, 477 U.S. at 322); *Heffron v. Adamar of N.J., Inc.*, 270 F.Supp.2d 562, 568–69 (D.N.J.2003). "If the non-movant's evidence on any essential element of the claims asserted is merely 'colorable' or is 'not significantly probative,' the court must enter summary judgment in favor of the moving party."

2006 WL 166452

Heffron, 270 F.Supp.2d at 69 (citing *Anderson*, 477 U.S. at 249–50).

III. Motion to Exclude Expert Daniel McDonald

Defendant moves to exclude the testimony of Plaintiffs' expert Daniel McDonald ("McDonald") on the grounds that he is unqualified and his report is unreliable.¹² Admissibility of expert testimony is governed by Federal Rule of Evidence 702 and the United States Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993).¹³ In the Third Circuit, the admissibility of expert testimony is contingent on the "qualifications" of the expert and the "reliability" of his methodology. *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717 (3d Cir.1994) (interpreting *Daubert*); see also *Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir.2000).

A. In Limine Hearing

In certain instances, courts are obligated to provide *in limine* hearings before applying *Daubert* to exclude expert testimony. *Padillas v. Stork-Gamco, Inc.*, 186 F.3d 412 (3d Cir.1999). A hearing is required, for example, where the court excludes an expert's conclusions on the grounds that they are "insufficiently explained and the reasons and foundations for them inadequately and perhaps confusingly explicated." *Id.* In other words, where a report is "conclusory and did not adequately explain the basis for [the expert's] opinion or the methodology employed in reaching his conclusions," the "plaintiff needs an 'opportunity to be heard' on the critical issues of scientific reliability and validity." *Oddi*, 234 F.3d 136, 152 (3d Cir.2000) (holding that the district court did not err "in granting summary judgment here without an *in limine* hearing") (quoting *Padillas*, 186 F.3d at 417). Where the evidentiary record is substantial, however, or the court has before it the information necessary to determine that the expert lacks "good grounds" for his conclusions, an *in limine* hearing may be unnecessary. *Id.* at 153.

*5 The evidence before this Court clearly establishes the process by which McDonald "arrived at his conclusions,"

Oddi, 234 F.3d at 152, and McDonald's report and deposition details the methodology underlying his determinations. As discussed below, this Court will exclude

McDonald's testimony on the grounds that his analysis and methodology are baseless and inconclusive, not because his report is insufficiently explained. Additionally, Defendant's motion for summary judgment alerted Plaintiffs to the *Daubert* challenge, yet Plaintiffs neither requested a hearing nor offered any affidavit or evidence in support of McDonald. Accordingly, an *in limine* hearing is unnecessary.

B. Qualifications

The Third Circuit instructs courts to "liberally" evaluate an expert's qualifications. *Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir.2000). In particular, the Circuit has "eschewed overly rigorous requirements of expertise and [has] been satisfied with more generalized qualifications."

In re Paoli, 35 F.3d at 741 (citing *Hammond v. International Harvester Co.*, 691 F.2d 646, 652–53 (3d Cir.1982) and *Knight v. Otis Elevator Co.*, 596 F.2d 84, 87–88 (3d Cir.1979)). This liberal treatment extends to the expert's substantive qualifications as well as his formal qualifications. *Id.*

Nevertheless, the Third Circuit has "also set a floor with respect to an expert witness's qualifications." *Elcock v. Kmart Corp.*, 233 F.3d 734, 742 (3d Cir.2000). To demonstrate when an expert would not be qualified under Rule 702, the *Elcock* Court offered the pre-*Daubert* case, *Aloe Coal Co. v. Clark Equip. Co.*, 816 F.2d 110 (3d Cir.1987), which held a tractor salesperson unqualified to testify as an expert about the cause of a tractor fire. *Elcock*, 233 F.3d at 742 (citing *Aloe Coal*, 816 F.2d 110).

In *Elcock* itself, the Court determined with "misgivings" that the district court had not abused its discretion by concluding that a psychologist with experience in obtaining employment for disabled individuals was qualified to testify to the possibility for vocational rehabilitation of the injured plaintiff. However, the Court acknowledged that it also would have upheld a decision to exclude the expert since "he seems most qualified to testify on a micro-level regarding the ability of a disabled individual to return to a specific job; he does not appear particularly qualified to testify on the macro-level regarding the number of jobs in the national or local economy that the disabled individual is able to perform."¹⁴ *Elcock*, 233 F.3d at 744. Taken together, *Elcock* and *Aloe Coal* indicate that where a proposed expert's area of experience is

2006 WL 166452

adjacent to, but not actually encompassing, the subject matter of his testimony, he may be deemed unqualified.

McDonald has worked as a licensed appraiser in New Jersey for approximately twenty-two years. Defendant argues that McDonald is nevertheless unqualified to testify to the diminution in value of Plaintiffs' properties because McDonald has no experience in appraising contaminated property. Defendant notes that McDonald has never appraised property allegedly contaminated by emissions from a gasoline station and has never acted as an expert in a situation involving contamination of the groundwater or allegations of a leaking underground storage tank. (Daniel McDonald Dep. ("McDonald Dep."), Mairo Cert. in Supp. Def.'s Mot. to Exclude Plaintiffs' Expert Daniel McDonald, Ex. C, at 23–24.) Defendant also points out that McDonald did not entirely understand the Ellwood and Gallo reports upon which he relied, including the charts indicating the presence and degree of contaminating agents on the property. (McDonald Dep. at 55–56.)

*6 This case lies squarely between *Aloe Coal* and *Elcock*. Although McDonald is an experienced appraiser, no evidence indicates that he has any experience appraising contaminated properties or is qualified to value the effects of stigma on property values. Just as a psychologist experienced in assisting individuals to find work may be unqualified to testify about the general availability of jobs in the economy, an individual able to appraise an uncontaminated property may have no grounds for appreciating the devaluation of the same property under unique conditions of contamination or stigma. Because nothing in McDonald's experience indicates knowledge or expertise in issues of contamination, he is unqualified to testify to the loss of value to Plaintiffs' properties arising from the alleged contamination.

C. Reliability

Because expert testimony has the potential to bear considerable weight with a jury, the district court functions as a gatekeeper responsible for assuring "that the scientific methodology upon which the expert opinion is founded is reliable" and that "the expert's conclusion is based on good grounds." *In re Paoli*, 35 F.3d at 732–33. To ascertain "reliability," the court must examine a number of factors, both those established in *Daubert* and those previously enumerated by the Third Circuit in *United States v. Downing*, 753 F.2d

1224 (3d Cir.1985). *Oddi*, 234 F.3d 145 (citing *Paoli II*, 35 F.3d at 742). In particular, the court must consider:

- (1) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Paoli II, 35 F.3d at 742 n. 8; *see also Elcock*, 233 F.3d at 746 (noting that "each factor need not be applied in every case"). The party wishing to introduce the testimony bears the burden of establishing "by a preponderance of the evidence that their opinions are reliable." *Paoli*, 35 F.3d at 744.

Of course, an expert's opinion need not be "perfect," and judges may not substitute their opinions for those of an expert. *Paoli*, 35 F.3d at 744; *see also Crowley v. Chait*, 322 F.Supp.2d 530, 536 (D.N.J.2004). However, courts also need not admit mere conclusions or "opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."

Magistrini v. One Hour Martinizing Dry Cleaning, 180 F.Supp.2d 584, 608 (D.N.J.2002) (quoting *General Elec. Co. v. Joiner*, 522 U.S. 136, 145–46, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)).

*7 Mere assumptions, without causal evidence or methodological analysis may be inadmissible. *In re TMI Litig.*, 193 F.3d 613, 667–68 (3d Cir.1999). Conclusions based only on the expert's experience, *Oddi*, 234 F.3d at 140–41, and testimony founded on methods that are not

2006 WL 166452

generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard, *Elcock*, 233 F.3d at 746. Furthermore, conclusions based on analogies that are too dissimilar to the subject of the testimony may also merit exclusion. *General Elec.*, 522 U.S. at 144 (rejecting expert testimony that plaintiff's cancer was due to exposure to PCBs when the testimony was based on animal studies of infant mice that had developed cancer after exposure to PCBs).

In response to Defendant's motion to exclude McDonald's testimony, Plaintiffs argue that "Mr. McDonald's opinions are based upon credible facts, NJDEP records, the reports of Plaintiffs' liability experts and individual appraisal reports prepared for each residential property." (Pl.s' Opp. Def.'s Mot. Summ. J. ("Opp."), filed Oct. 12, 2005, at 30.) However, McDonald testified in his deposition that he relied only on the Gallo and Ellwood Reports, and he specifically testifies that he did *not* "review any correspondence from the NJDEP related to this site." (McDonald Dep. at 15.)¹⁵

In spite of Plaintiffs' arguments to the contrary, this Court cannot avoid the conclusion that McDonald's methodology is entirely unreliable. In his report, McDonald determines that the value of Plaintiffs' properties with no evidence of contamination should be discounted 35% percent and property with onsite contamination should be discounted by 66%. (McDonald Report ("McDonald Report"), Mairo Cert. in Support of Def.'s Mot. Exclude Pl.s' Expert Daniel McDonald, Ex. B., at 31, 33.) McDonald reached the 35% and 66% figures without discussing, or even recognizing, the extent to which the property was actually contaminated. As demonstrated by his ignorance of the "ND"/Not Detected signifier in the Gallo and Ellwood Reports, McDonald did not know how to read the charts denoting the levels of contamination. (McDonald Dep. at 56.) Nor had McDonald ever conducted any physical inspection of or visit to the properties prior to writing the report.¹⁶ (McDonald Dep. at 15–16.)

Furthermore, to quantify the stigma attached to Plaintiffs' properties, McDonald relies upon a highly misleading analogy with a site of profoundly contaminated residential properties in Dover Township. (McDonald Report at 27.) Specifically, McDonald compares Plaintiffs' properties with "an area of Dover Township that had ground water contamination from Union Carbide and ... Ciba Geigy that resulted in what was commonly known as a cancer cluster among children," meaning "an inordinate number of children

with cancer." (McDonald Dep. at 158–59.) McDonald selected the Dover site not because of its comparability, but because McDonald "didn't know of any other cases that, where the data was as readily available." (McDonald Dep. at 159.)

*8 Employing the Dover analogy, McDonald determined that the property in the Dover site is in the final stages of recovery and continues to suffer a stigma loss of 13%. Because McDonald considered Plaintiffs' properties in the early stages of recovery, McDonald determined that they must bear a stigma discount of at least two or three times that of the Dover site, resulting in a discount of 35%.¹⁷ However, the severity of the contamination and resulting illness among Dover residents undercuts any grounds for comparison with Plaintiffs' properties where there were few detections of contaminants and no reported physiological effects.

The methodology employed to reach the 66% figure is equally unreliable. To assess the value of properties with some evidence of contamination, McDonald sent an email to thirteen financial lenders to determine whether they would "lend on a property that has known contamination, or the stigma of contamination, to the ground water." (McDonald Report at 32.) Of the thirteen lenders, six replied. One of those refused to comment, and one said that it would loan given certain circumstances. The other four lenders stated that they would not lend on a property that is contaminated, but the content of their brief responses suggested that they understood the email hypothetical to denote property that was actually contaminated and out of compliance with state requirements.¹⁸

From the results of the email test, McDonald concludes that there would be no buyers other than those who could pay cash.¹⁹ McDonald then assessed the discount in value given cash-only buyers, extrapolating from this a discount of 66%. (McDonald Report at 33.) However, the reliability of the 66% figure is entirely invalidated by the overemphasis placed on the four responses to the email hypothetical, the misleading implication in the email hypothetical, suggesting a much greater contamination of the property than actually present, and the unclear calculations and assumptions underlying McDonald's arrival at 66%.

Ultimately, McDonald's report does not fulfil any of the reliability factors. His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any

2006 WL 166452

real standards. Because McDonald is unqualified and his evaluation is unreliable, Defendant's motion *in limine* to exclude his testimony will be granted.

IV. Plaintiffs' Claims

A. Negligence and Gross Negligence

To surmount a motion for summary judgment of a negligence claim, Plaintiffs must provide evidence such that a reasonable jury could find "breach of a duty of care and actual damages sustained as a proximate cause of the breach." *Muise v. GPU, Inc.*, 371 N.J.Super. 13, 35, 851 A.2d 799 (App.Div.2004) (citing *Weinberg v. Dinger*, 106 N.J. 469, 484, 524 A.2d 366 (1987)); *Nappe v. Anschelewitz, Barr, Ansell & Bonello*, 97 N.J. 37, 45, 477 A.2d 1224 (1984) ("[T]he plaintiff must show a breach of duty and resulting damage to prevail in a negligence action."). Motiva argues that Plaintiffs have failed to establish damages and causation and requests summary judgment of Plaintiffs' gross negligence claim on the same basis.²⁰

*9 The absence of an injury will preclude a negligence claim, even where a clear breach of duty is present. *Rocci v. MacDonald-Cartier*, 323 N.J.Super. 18, 24–25, 731 A.2d 1205 (App.Div.1999) (affirming summary judgment for insufficient evidence of damages in defamation case and noting that "a plaintiff must present proof of a material question of fact as to both liability and damages") (citing *Norwood Easthill Assoc. v. Norwood Easthill Watch*, 222 N.J.Super. 378, 384, 536 A.2d 1317 (App.Div.1988) (affirming summary judgment of malicious interference claim on basis that "plaintiff has suffered no injury or damage")). At the summary judgment stage, Plaintiffs must provide actual evidence of injury and cannot simply rely upon "unsubstantiated allegations." *Trap Rock Indus., Inc. v. Local 825*, 982 F.2d 884, 890 (3d Cir.1992) (reversing district court's denial of summary judgment). Just as "a residential customer not in residence during a power loss, or a commercial customer whose store was closed, might have no damages except the inconvenience of resetting clocks," *Muise*, 371 N.J.Super. at 49, 851 A.2d 799, the release of contaminants into the groundwater aquifer does not itself generate damages, unless Plaintiffs can show that they suffered harm.

Plaintiffs concede that they "have not presented and will not present claims for the present manifested bodily

injury." (Undisputed Facts ¶ 67.) However, they argue that they have adequately established damages for medical monitoring and property damage. They do not address their claim for emotional distress.²¹

1. Medical Monitoring

Damages for medical monitoring are appropriate where a plaintiff exhibits no physical injury, but nevertheless requires medical testing as a proximate result of a defendant's negligent conduct. *Ayers v. Jackson Twp.*, 106 N.J. 557, 600, 525 A.2d 287 (1987). The risk of injury need not be quantified to merit medical surveillance damages; however, the plaintiff must establish that the risk of serious disease is "significant." *Id.* at 599–600, 525 A.2d 287; *Campo v. Tama*, 133 N.J. 123, 131, 627 A.2d 135 (1993) (awarding medical monitoring damages to a plaintiff with a "fifty-to-seventy-five-percent chance of suffering a recurrence of cancer" due to the delay resulting from defendant doctor's malpractice). In the case of toxic exposure, "medical-surveillance damages may be awarded only if a plaintiff reasonably shows that medical surveillance is required because the exposure caused a distinctive increased risk of future injury." *Theer v. Philip Carey Co.*, 133 N.J. 610, 627, 628 A.2d 724 (1993). Such damages are "not available for plaintiffs who have not experienced direct and hence discrete exposure to a toxic substance and who have not suffered an injury or condition resulting from that exposure." *Id.* at 628, 628 A.2d 724.

Low level contamination, "that is, contamination below the minimum level set by DEP for water remediation," typically is insufficient to establish injurious toxic exposure.

Muralo Co., Inc. v. Employers Ins. of Wausau, 334 N.J.Super. 282, 290–291, 759 A.2d 348 (App.Div.2000) ("[S]ince it is clear that no untreated groundwater is ever entirely pure, we are satisfied that DEP standards are the most reliable guide for determining whether contamination causing damage ... has occurred."). Here, contaminants have been detected in only eight of Plaintiffs' wells, and no detection has been even close to the GWQS. The NJDEP never restricted Plaintiffs' use of water from their potable wells, nor required Defendant to treat Plaintiffs' wells or to provide Plaintiffs with an alternate water source.

*10 Plaintiffs rely on the testimony of Dr. Michael Gochfeld, Ph.D. ("Gochfeld"), to establish the significant health risks

2006 WL 166452

and necessity of medical surveillance following from the alleged contamination of Plaintiffs' property. However, nothing in Gochfeld's report concludes that the individual Plaintiffs themselves require medical monitoring under the circumstances. Rather, Gochfeld's report creates a medical monitoring program for a hypothetical target population without taking into consideration the actual exposure of any plaintiff.²² (Gochfeld Dep. at 26–29.) Gochfeld prepared his report under the assumption that “there were known or actual or potential exposure to a variety of constituents of gasoline.” (Gochfeld Dep. at 12.) He states in deposition that he had “no specific factual knowledge of the actual exposures in this case,” and he confirms that he has never examined the individual Plaintiffs. (Gochfeld Dep. at 10, 29.)

Gochfeld himself notes that “[w]hether a person exposed to MTBE requires medical monitoring depends in large measure on the level of exposure and the time over which it occurred” and notes that “clearly people that are exposed to MTBE casually would not require one.” (Gochfeld Dep. at 24.) Furthermore, Gochfeld stated that he “probably would not” recommend medical monitoring for the minor and often single detections of MTBE on Plaintiffs' properties.²³ (Gochfeld Dep. at 46–50.) Consequently, Gochfeld's report does not establish that Plaintiffs require medical monitoring.

Plaintiffs also appear to argue that their wells may have been more contaminated prior to the initiation of Defendant's testing in July 2000. (Opp. at 20.) However, Plaintiffs provide no evidence suggesting that such exposure actually occurred or that any exposure prior to July 2000 was more than minimal. Plaintiffs also argue for the first time in their Opposition that they may have ingested water from contaminated sources besides the potable wells on their property. (Opp. at 20.) However, Plaintiffs offer no evidence that any Plaintiff actually consumed water from CW–8. Without any evidence supporting their theories, Plaintiffs cannot establish a claim for medical monitoring sufficient to survive summary judgment.

Because Plaintiffs have provided no evidence of a “distinctive increased risk of future injury” from the exposure, Plaintiffs are not entitled to damages for medical monitoring.

2. Property Damage

Defendant requests summary judgment of Plaintiffs' claims of property damage on the grounds that the contamination caused no actual damage to Plaintiffs' properties.²⁴ Instead of

claiming that their property was physically harmed, Plaintiffs contend that the news of the contamination stigmatized their property, reducing its value in the minds of potential buyers.

In support of their claim for stigma damages, Plaintiffs offer the expert testimony of Daniel McDonald. However, as discussed previously, McDonald's testimony must be excluded as unreliable. Plaintiffs also argue that the testimony of individual Plaintiffs establishes a stigma discount to their property:

*11 Plaintiff Marie Wallace has submitted sworn Interrogatory statements documenting a \$150,000.00 loss on the sale of her property. See Exhibit 0 to McKenna Certification. Other Plaintiffs have similarly provided certified answers to Interrogatories and Deposition testimony as to the loss in value through sales transactions, which occurred from the discharge. See Exhibit N–R to the McKenna Certification.

(Opp. at 20–21.)

This evidence fails to establish an injury. Exhibits N–R consist of contracts for sale and unexecuted contracts for sale of three of Plaintiffs' properties, including the Wallace property, leaving it to the Court's imagination to ascertain how these contracts demonstrate a loss in value. Wallace's testimony also fails to establish a stigma injury to the property.

Specifically, Wallace claims that she received a verbal offer for her asking price of \$500,000.00 from a man named “Amin,” whose last name she cannot recall. (Marie Wallace Dep., McKenna Cert., Ex. 0, M.) Wallace claims that he reneged from the agreement after she told him about the release, however, the alleged offeror never gave Wallace the offer in writing and she has no evidence of the offer or “Amin's” motive for withdrawing, aside from her own testimony. Consequently, even construing this evidence in the light most favorable to Plaintiffs, no reasonable jury could find that Plaintiffs' properties were stigmatized on the basis of this evidence alone.

2006 WL 166452

3. Emotional Distress

Defendant also moves for summary judgment of Plaintiffs' claim for emotional distress. Plaintiffs do not respond to this argument in their Opposition, and Defendant is entitled to summary judgment of Plaintiffs' emotional distress claim for Plaintiffs' failure to present evidence of significant distress or physical injury.

A claim for emotional distress cannot succeed absent evidence of physical injury or "severe and substantial" emotional distress, even where a person has a reasonable concern of an enhanced risk of future disease. *Ironbound Health Rights Advisory Com'n v. Diamond Shamrock Chem. Co.*, 243 N.J.Super. 170, 174–75, 578 A.2d 1248 (App.Div.1990) (noting that "[i]n the absence of physical injury, damages are allowed where the resultant emotional distress is severe and substantial" and listing cases). Without some physical injury, mere exposure to toxic chemicals does not give rise to a claim for emotional distress damages. *Id.* (holding plaintiffs unable to sustain emotional distress claim for exposure to chemicals manufactured at plant near their residences); see also *Mauro v. Raymark Indus., Inc.*, 116 N.J. 126, 137, 561 A.2d 257 (1989); *Troum v. Newark Beth Israel Med. Ctr.*, 338 N.J.Super. 1, 17, 768 A.2d 177 (App.Div.2001). Because Plaintiffs provided no evidence of significant emotional distress or physical injury, Defendant's motion for summary judgment will be granted.

B. Trespass

Defendant moves for summary judgment of Plaintiffs' claim for trespass. Plaintiffs argue that Defendant's "intentional refusal" to remove the contamination from their property and failure to install remediation equipment amounts to an intentional trespass.²⁵ (Opp. at 25.)

*12 The Restatement (Second) of Torts defines intentional trespass as:

One who intentionally and without a consensual or other privilege

(a) enters land in possession of another or any part thereof or causes a thing or third person so to do, or

(b) remains thereon, or

(c) permits to remain thereon a thing which the actor or his predecessor in legal interest brought thereon in the manner

stated in §§ 160 and 161, is liable as a trespasser to the other irrespective of whether harm is thereby caused to any of his legally protected interests.

Rest. (2d) Torts § 158.

As Defendant argues, New Jersey has moved away from "such common law claims as trespass and nuisance" in environmental pollution cases. *Mayor and Council of Borough of Rockaway v. Klockner & Klockner*, 811 F.Supp. 1039, 1053 (D.N.J.1993); *Kenney v. Scientific, Inc.*, 204 N.J.Super. 228, 256, 497 A.2d 1310 (1985) ("There is no need for us ... to torture old remedies to fit factual patterns not contemplated when those remedies were fashioned."). Regardless of the continuing viability of trespass claims in the environmental context, however, Plaintiffs have failed to come forward with any evidence supporting their claim and cannot survive summary judgment.

Plaintiffs note that they are "not arguing that Defendants intentionally caused the contamination of their property," but rather are claiming that "defendants have repeatedly refused to perform the horizontal and vertical delineation of the soil and groundwater contamination in the area of the residential properties." (Opp. at 25.) However, no evidence suggests that such measures were necessary to remove contaminants from Plaintiffs' properties. Rather, the record indicates that Defendant consistently complied with NJDEP requirements, including the installation and maintenance of a groundwater recovery system to rehabilitate the aquifer, and the NJDEP never required Defendant to install any sort of remediation equipment on any of the residences. Given that there has been no detection of a gasoline-related contaminant in any Plaintiff's potable well since April 2001, the argument that Defendant permitted contamination to remain on Plaintiffs' properties lacks any viable evidentiary foundation. Defendant's motion for summary judgment of Plaintiffs' trespass claim will be granted.

C. Strict Liability

Plaintiffs originally claimed a cause of action for strict liability under the theory that the handling, storage, or use of gasoline constitutes an abnormally dangerous activity. However, Plaintiffs voluntarily dismissed this claim in their Opposition. (Pl.'s Opp. at 3.) Accordingly, the Court will not address the merits of Plaintiffs' strict liability claim.

2006 WL 166452

D. Environmental Statutes

1. New Jersey Environmental Rights Act

Plaintiffs allege a right to recover under the New Jersey Environmental Rights Act ("ERA"), N.J.S.A. 2A:35A-1 *et seq.* Defendant requests summary judgment on the grounds that Plaintiffs have not satisfied the ERA's notice provision, N.J.S.A. 2A:35A-11, and that an ERA claim is not actionable where the NJDEP has acted to institute and oversee remediation of the contamination.

*13 Section 4(a) of the ERA, permits "any person" to "maintain an action in a court of competent jurisdiction against any other person to enforce, or to restrain the violation of, any statute, regulation or ordinance which is designed to prevent or minimize pollution, impairment or destruction of the environment." N.J.S.A. 2A:35A-4(a). Although the ERA itself does not create substantive rights, it confers standing on private persons to enforce other environmental statutes, including the New Jersey Spill Compensation and Control Act ("Spill Act"). *Rockaway*, 811 F.Supp. at 1054; *Allied Corp. v. Frola*, 701 F.Supp. 1084, 1091 (D.N.J.1988).

The NJDEP is "entrusted initially with the right to determine the primary course of action to be taken." *Howell Township v. Waste Disposal, Inc.*, 207 N.J.Super. 80, 95, 504 A.2d 19 (App.Div.1986) ("In order to be effective, [the NJDEP] must normally be free to determine what solution will best resolve a problem on a state or regional basis given its expertise and ability to view those problems and solutions broadly."). Consequently, the right of private parties to sue under the EPA is "an alternative to inaction by the government which retains primary prosecutorial responsibility." *Superior Air Prod. Co. v. NL Indus., Inc.*, 216 N.J.Super. 46, 58, 522 A.2d 1025 (App.Div.1987); *Rockaway*, 811 F.Supp. at 1054 ("[T]he primary goal of the ERA is to limit lawsuits by private litigants to those instances where the government has not acted.").

A private ERA suit may be permitted even in the absence of complete government inaction if the NJDEP has "failed in its mission ... failed or neglected to act in the best interest of the citizenry or has arbitrarily, capriciously or unreasonably acted." *Howell*, 207 N.J.Super. at 96, 504 A.2d 19; *Morris County Transfer Station, Inc. v. Frank's Sanitation Serv., Inc.*, 260 N.J.Super. 570, 578, 617 A.2d 291 (App.Div.1992) (permitting private ERA

action where the NJDEP would not address violation for three years and had taken no enforcement actions against contaminating defendant who continued operating its illegal facility two months after receiving a violation notice). Where NJDEP "action subsequently proves sufficient to protect the environment," however, NJDEP "action under the Spill Act is preemptive of private rights under ERA." *Superior Air Prod.*, 216 N.J.Super. at 61, 522 A.2d 1025. The permissibility of private action must be evaluated on a case-by-case basis. *Id.*

Here the record indicates consistent and pervasive NJDEP oversight of the remediation process, requiring Defendant to regularly test Plaintiffs' wells and institute interim and permanent groundwater recovery systems. Plaintiffs have not claimed that the NJDEP failed to act or acted unreasonably, and there are no grounds for finding NJDEP inaction sufficient to permit a private ERA suit. Furthermore, as discussed below, Plaintiffs failed to give the NJDEP the requisite notice of their private suit. Accordingly, Defendant's motion for summary judgment of Plaintiffs' ERA claim will be granted.

2. Notice

*14 Before a private party may commence an action under the ERA, the party must "at least 30 days prior to the commencement thereof, direct a written notice of such intention by certified mail, to the Attorney General, the Department of Environmental Protection, the governing body of the municipality in which the alleged conduct has, or is likely to occur, and to the intended defendant." N.J.S.A. 2A:35A-11. The notice provision is intended to give the government an adequate opportunity to intervene in the litigation and to allow the NJDEP:

to exercise value judgments in individual cases, e.g., whether it will join in that litigation or enforcement proceeding, whether other actions it may have taken already with respect to the particular problem or offender would render the litigation subject to collateral estoppel or res judicata principles, whether its expertise would assist the court, whether broad State interests would be sacrificed unduly to

2006 WL 166452

regional or personal interests by the instigators of that litigation, etc.

Howell, 504 A.2d at 95; *Morris County*, 260 N.J.Super. at 578, 617 A.2d 291 (quoting *Howell* for same).

Because Plaintiffs did not provide the required thirty day notice to the NJDEP or the Attorney General, they are barred from further pursuing their claim under the ERA. Plaintiffs argue that Defendant is judicially estopped from claiming lack of notice for failure to raise this issue at an earlier stage in the case. Plaintiffs analogize the ERA requirement to that of an affidavit of merit, required in certain cases to avoid “unmeritorious and frivolous malpractice lawsuits at an early stage of litigation.” *Knorr v. Smeal*, 178 N.J. 169, 197–98, 836 A.2d 794 (2003) (holding judicially estopped defendant's request for summary judgment for plaintiff's failure to file affidavit of merit) (citing *Palanque v. Lambert–Woolley*, 168 N.J. 398, 404, 774 A.2d 501, 505 (2001)); *Ferreira v. Rancocas Orthopedic Assoc.*, 178 N.J. 144, 836 A.2d 779, (2003) (same).

Defendant argues that the ERA notice requirement is more analogous to the notice of intent in the Resource Conservation and Recovery Act (RCRA), which the Supreme Court held to be a jurisdictional prerequisite to suit in *Hallstrom v. Tillamook County*, 493 U.S. 20, 31, 110 S.Ct. 304, 107 L.Ed.2d 237 (1989) (“[C]ompliance with the 60–day notice provision is a mandatory, not optional, condition precedent for suit.”); *Public Interest Research Group of N.J., Inc. v. Windall*, 51 F.3d 1179, 1189 (3d Cir.1995) (holding notice provision jurisdictional in context of Clean Water Act (“CWA”)); *Hawksbill Sea Turtle v. Federal Emergency Mgmt. Agency*, 126 F.3d 461, 471 (3d Cir.1997) (holding notice provision jurisdictional in context of Endangered Species Act (“ESA”)).

However, the language of the notice requirement in RCRA is not entirely analogous to that of the ERA. RCRA states, under the heading of “Actions prohibited” that “No action may be commenced ... prior to 60 days after the plaintiff has given notice of the violation to” the Administrator, the state and the alleged violator. 42 U.S.C.A. § 6972. The ERA lacks the “no action may be commenced” language of the RCRA, CWA, and ESA, and states only that notice must be sent “at least

30 days prior to the commencement” of suit. Consequently, the argument that the plain language of the statute creates a jurisdictional bar is not as strong in the context of the ERA.

*15 Nevertheless, because the purpose of the notice provision is to provide the Attorney General and NJDEP with notice of the suit and opportunity to intervene, *Howell*, 504 A.2d at 95, and not merely to protect defendants, as in the case of the affidavit of merit, Defendant is not judicially estopped from raising Plaintiffs' lack of compliance with the notice provision and is entitled to summary judgment of Plaintiffs' ERA claim.

E. Spill Act Claim

In their complaint, Plaintiffs assert a private right of action under the Spill Act, N.J.S.A. 58:10–23.11 *et seq.*²⁶ As amended in 1991, the Spill Act authorizes a private cause of action for individuals to recover costs for environmental damage to their property. *Housing Auth. of City of New Brunswick v. Suydam Inv., L.L.C.*, 177 N.J. 2, 18, 826 A.2d 673 (2003). Actions under the Spill Act are limited to clean up and removal costs, *Bahrle v. Exxon Corp.*, 145 N.J. 144, 155, 678 A.2d 225 (1996), defined as:

all direct costs associated with a discharge, and those indirect costs that may be imposed by the department pursuant to section 1 of P.L.2002, c. 37 associated with a discharge, incurred by the State or its political subdivisions or their agents or any person with written approval from the department in the: (1) removal or attempted removal of hazardous substances, or (2) taking of reasonable measures to prevent or mitigate damage to the public health, safety, or welfare, including, but not limited to, public and private property.

N.J.S.A. 58:10–23.11b(d). The Act does not authorize “damages arising from emotional distress, enhanced risk of disease, loss of enjoyment of property, and other economic and financial harm.” *Bahrle*, 145 N.J. at 155, 678 A.2d 225. Plaintiffs maintain that the investigation conducted by Ellwood was a reimbursable clean up and removal cost under the Spill Act. As Plaintiffs suggest, because “a discharge cannot be addressed until the contaminants are defined and the extent of the discharge determined,” certain forms of investigative costs are implicitly included in the Act.

Metex Corp. v. Federal Ins. Co., 290 N.J.Super. 95, 115, 675 A.2d 220 (App.Div.1996).

2006 WL 166452

However, for a private party to obtain reimbursement under the Act, the party must have obtained "written approval from the department," for example, in a memorandum of agreement, prior to incurring the cost. N.J.S.A. 58:10–23.11b(d); *Id.* Such approval permits the NJDEP to "review and approve or disapprove its investigation to date, its proposed remedial action, and its report of the implementation of its action." *Id.*; see also *Interfaith Cmty Org. v. Honeywell Intern., Inc.*, 263 F.Supp.2d 796, 867 (D.N.J.2003) (concluding "that such costs were approved by and/or incurred at the direction of NJDEP and thus are recoverable

under the Spill Act."). Because Plaintiffs have not obtained NJDEP approval for any cost incurred, including the Ellwood report, Defendant is entitled to summary judgment of Plaintiffs' Spill Act Claim.

*16 The accompanying Order shall enter today.

Elcock, 233 F.3d at 741.

All Citations

Not Reported in F.Supp.2d, 2006 WL 166452

Footnotes

- 1 The following facts are taken from Defendant's statement of undisputed material facts, filed June 24, 2005, ("Undisputed Facts") and Plaintiffs' counterstatement of undisputed facts, filed Oct. 14, 2005, ("Counterstatement Facts"). Plaintiffs did not provide a separate statement of undisputed facts. Although Plaintiffs dispute the majority of Defendant's statements of fact, Plaintiffs' counterstatements typically provide additional facts without setting forth any conflicting evidence. Where no actual disputes are presented, Defendant's statements will be treated as undisputed. See e.g., *Tofano v. Reidel*, 61 F.Supp.2d 289, 292 n. 1 (D.N.J.1999) (citing Fed.R.Civ.P. 56(e)) ("This court will ... not consider assertions without evidential support as creating genuine issues of disputed fact."); *Talbot v. United States*, 2005 WL 2917463, *2 (D.N.J.2005) (noting that where the nonmoving party does not submit facts in opposition, "it is entirely appropriate for this court to treat all facts properly supported by the movant to be uncontroverted") (quoting *Allebach v. Sherrer*, No. 04–287, 2005 U.S. Dist. LEXIS 15626, at *5 (D.N.J.2005)). More generally, Plaintiffs' brief suffers from numerous typographical errors and a dearth of citations to page numbers in the record. This "alone warrants exclusion of the evidence." See *Orr v. Bank of America, NT & SA*, 285 F.3d 764, 774–75 (9th Cir.2002) (holding that party's failure to cite page and line numbers when referencing the deposition merits exclusion of evidence); *Huey v. UPS, Inc.*, 165 F.3d 1084, 1085 (7th Cir.1999) ("[J]udges need not paw over the files without assistance from the parties."); *Nissho-Iwai Am. Corp. v. Kline*, 845 F.2d 1300, 1307 (5th Cir.1988) (parties must designate specific facts and their location in the record).
- 2 Among the original litigants to the suit were also former plaintiffs Michael and Susan Kammerhoff and Norma Simmons. The Kammerhoff plaintiffs were voluntarily dismissed, and plaintiff Norma Simmons died on August 26, 2000.
- 3 VOCs generally associated with gasoline discharge include MTBE, benzene, toluene, ethylbenzene, xylene (collectively "BTEX"), and tertiary butyl alcohol ("TBA"). The NJDEP has issued a Ground Water Quality Standard ("GWQS") for each of these VOCs, also known as "gasoline-related compounds." MTBE, for example, has a GWQS of 70 parts per billion ("ppb").
- 4 Although Motiva detected MTBE in thirteen residential wells, not all of these wells are owned by Plaintiffs to this litigation. Of the twenty-seven parcels of property at issue in this suit, only eight of the properties contain wells that ever tested positive for any gasoline-related compound.
- 5 The direction of water's flow in an aquifer is described as "downgradient," and the direction against the current is "upgradient."

2006 WL 166452

- 6 In particular, testing revealed emissions in monitoring wells 6–Shallow (“MW–6S”) and 7–Deep (“MW–7D”), which lie between the Motiva site and the residential properties. However, the majority of upgradient monitoring wells did not test positive for gasoline-related contaminants. (NJDEP Directive, March 21, 2001 (“March 2001 Directive”), Mairo Cert. in Supp. Def.’s Mot. Summ. J., filed June 24, 2005 (“Mairo Cert.”), Ex. O, at 4.)
- 7 Plaintiffs dispute Defendant’s characterization of the CEA, (Counterstatement Facts ¶ 31), on the basis that Defendant proposed the CEA prior to conducting an actual delineation of the plume and that “the Plaintiffs’ residential wells could only had [sic] been included in the CEA, if Defendant intended to supply a permanent public water supply to Plaintiffs’ properties.” While Plaintiffs’ contention with the CEA is not entirely clear, Plaintiffs have not provided any evidence indicating that the NJDEP improperly approved the CEA or that the CEA was an inaccurate representation of the boundaries of contaminants in excess of the GWQS.
- 8 Plaintiffs’ properties are: 850 Sicklerville Road; 565, 569, 581, and 583 Berlin–Cross Keys Road; 6, 9, 10, 12, 13, 14, 1, 16, 17, 18, 20 Spring Hollow; 2, 4, 6, and 8 Latham Way; 3, 4, 5, 7, 12, 14, and 15 Donna Marie Court.
- 9 CW–8 is located approximately 1,000 feet downgradient of the contamination site. (March 2001 Directive at 2.) While active, CW–8 pumps approximately 500 gallons per minute and causes the groundwater to flow southwest. (Ellwood Report at 2.) When CW–8 is not pumping, the groundwater flow is more westerly. (Ellwood Report at 2.)
- 10 Plaintiff disputes these facts on the basis that:
 The Defendant has no data for any portable [sic] water supply of the Plaintiffs prior to July 2000. The Defendant never performed any delineation of the groundwater plume in the areas of the residential properties despite having actual knowledge of such contamination in MW–6, MW–7 and MW–12. See Gallo Certification and Exhibits C, D and E.
 (Counterstatement Facts ¶¶ 46–48.) However, because Defendant makes no averment of the presence or absence of contamination prior to July 2000, Defendant’s statements are not actually in dispute. Plaintiffs provide no fact indicating an inaccuracy in Defendant’s statements regarding the testing of Plaintiffs’ wells. Consequently, there is no actual dispute regarding the presence or amount of *detected* gasoline-related compounds.
- 11 Plaintiffs dispute these statements by citing to Exhibit F of the McKenna certification; however, Exhibit F is the Ellwood report and therefore is not indicative of the NJDEP requirements. Plaintiffs nowhere cite to a statement by the NJDEP requiring Defendant to treat their water or provide them with an alternate water source, and therefore this fact is undisputed.
- 12 Because this Court will grant Defendant’s motion for summary judgment, it will not reach the merits of Defendant’s motions to exclude experts Gochfeld, Ellwood, and Gallo.
- 13 After *Daubert*, Rule 702 was amended to encompass the *Daubert* analysis:
 If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.
 Fed.R.Evid. 702. While *Daubert* itself addressed only the admissibility of scientific evidence, the Court has since noted that courts’ gatekeeping obligations extend to all expert testimony. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).
- 14 The Court noted that it had “misgivings” about the expert’s qualifications in spite of:
 (1) [the expert’s] general training in “assessing” individuals, which he received while earning his Ph.D. in psychology; (2) his experience, twenty years previous, helping drug addicts reenter the workforce; (3) his experience primarily in the last two years dealing with the Virgin Islands Division of Workers’ Compensation, which he had advised regarding the ability of approximately fifty to sixty-five disabled employees to return to their previous jobs; (4) his past experience as an expert witness making lost earning capacity assessments;

2006 WL 166452

(5) his attendance at two seminars regarding vocational rehabilitation, and his stated familiarity with the literature in the area; (6) his membership in two vocational rehabilitation organizations, both of which place no restrictions on membership; and (7) the fact that when [the expert] was in school, a degree in vocational rehabilitation therapy was not available, but that he received similar training nonetheless.

15 Plaintiffs also argue that "Defendant does not attack the methodology, standard or factual basis for the opinions," (Opp. at 31), however, it is quite clear from Defendant's motion that the reliability of McDonald's methodology is hotly disputed.

16 McDonald also appeared unaware of the fact that Plaintiffs' properties are served by potable wells, even though the potable wells contain the evidence of contamination.

Q: Do you know whether or not the plaintiffs' properties have potable wells?

A: It's my understanding that they are hooked to a public water system.

Q: If each of the properties did in fact have a potable well, would that be a factor that you were consider relevant in your analysis?

Mr. McKenna: You may want to review the documents that you referenced in your report to assist you in this area. Just separate the Ellwood and Gallo reports. I'm going to go to the men's room.

(Whereupon, a recess is taken.)

Mr. Mairo: I am going to object that Mr. McKenna was basically coaching the witness.

Back on the record.

A: Your question about whether or not each of these houses were, was, had their own private well on site-

Q: Uh-huh?

A: -it's my understanding that each house is served by wells within and around the neighborhood and that Consumer, Consumers Water Company owns those wells and supplies that water to the homes.

(McDonald Dep. at 36.)

17 McDonald reaches the 35% devaluation figure with the following methodology:

The subject properties are in the early stages of monitoring, and clean up of the ground water contamination. The properties from Dover Twp. are beyond the clean up stage and into the final stage of recovery, yet they still show a 13% loss in value as compared to similar properties outside of the contaminated area. The subject area is in stage D of recovery, which is the beginning of the remediation process. Based on the acceptance of the Detrimental Condition Model as a viable process for valuing Detrimental Conditions to Real Estate, by the appraisal community and the Subcommittee on Housing and Community Opportunity of the House Committee on Financial Services, it would be logical to assume that the discount to the properties which are the subject of this report, would be 2 to 3 times that of properties in the final stage of recovery. In this case a discount of 35% would be considered reasonable.

(McDonald Report at 31.)

18 Interbay Funding, for example, qualified their statement that they would not lend by noting, "The property would have to be completely cleaned up. They would have to file all necessary documents to the state of NJ and we would require something from the state telling us the property is cleaned up." (McDonald Report at 32.) From this, McDonald concluded that Interbay Funding would not lend on properties such as Plaintiffs', without considering that none of Plaintiffs' properties were contaminated in excess of state standards.

19 In evaluating this data, McDonald states:

The lenders that did respond have overwhelmingly stated that they would not approve the loan at all, or they would require substantial conditions to the loan. In the case of the subject properties, it can be assumed that a purchaser with private financing or cash would be the only potential buyer of houses in this area.

(McDonald Report at 32.)

20 Because the Court now finds that there is no evidence of any actual injury arising from Defendant's negligence, this Court will not address Defendant's causation argument.

21 Plaintiff argues that Defendant's motion for summary judgment of its negligence claim should be denied on the basis of the doctrine of *res ipsa loquitur*. However, *res ipsa loquitur* acts only to "permit[] an inference of defendant's negligence" (i.e., that defendant acted in an unreasonable manner) under particular

circumstances. *Jerista v. Murray*, 185 N.J. 175, 192, 883 A.2d 350 (2005). The doctrine does not establish either causation or the presence of damages. See e.g., *Bahrle v. Exxon Corp.*, 279 N.J. Super. 5, 35, 652 A.2d 178 (App.Div.1995) (holding *res ipsa* doctrine inapplicable where "there was a factual dispute as to whether the contamination was a result of plaintiffs' own voluntary acts or neglect"). Accordingly, because Defendant is contesting only causation and damages, the *res ipsa* doctrine does not apply.

22 Gochfeld testifies in his deposition that he created his report without any specific information about the Plaintiffs:

Q: So, for example, in determining the percentage of the target population that was in high exposure category, that wasn't based on the ground water, your review of the ground water tables that were attached to Mr. Gallo's report?

A: It was not.

Q: That was based purely on just an assumption of yours?

A: It was an assumption based on experience with previous programs or programs that are currently underway in our communities.

Q: Having no specific factual knowledge of the actual exposures in this case?

A: That's correct, these are hypotheticals.

(Gochfeld Dep. at 28–29.)

23 Gochfeld also states that he would not even recommend medical monitoring for the one property with by far the highest detection of MTBE (13.8 ppb at 4 Latham Way) "on this data alone" because "[i]t is possible that a person living there would only be drinking bottled water, would not be in the house very much." (Gochfeld Dep. at 50.)

24 Defendant argues further that New Jersey law does not permit Plaintiffs to recover for stigma damages in the absence of some physical harm to their property. Because Plaintiffs have provided no evidence of any stigma to their property, the Court will not reach Defendant's alternative argument.

25 It is unclear whether Plaintiffs allege negligent trespass since they discuss only the Restatement (Second) of Torts § 158, Intentional Trespass, in their Opposition. Unlike intentional trespass, negligent or reckless trespass requires evidence of "harm to the land, to the possessor, or to a thing or a third person." Rest.

Torts 2d § 165; see also *Burke v. Briggs*, 239 N.J. Super. 269, 271, 571 A.2d 296 (App.Div.1990) (citing Rest.2d Torts § 158 with approval for another premise); *Karpjak v. Russo*, 450 Pa. Super. 471, 481, 676 A.2d 270 (Pa. Super.1996) (affirming dismissal of trespass claim for entry of dust onto property since the "evidence failed to establish that the dust caused appellants harm"). As discussed previously, Plaintiffs have not provided any evidence of injury to their persons or property. Consequently, to the extent that Plaintiffs are claiming negligent trespass, Defendant is entitled to summary judgment.

26 It is unclear whether Plaintiffs also raise a claim for cleanup and removal costs from the Spill Compensation

Fund under N.J.S.A. 58:10–23.11g(a). (Opp. at 12–13.) However, the appropriate procedure to obtain compensation under the Fund is by filing a claim with the administrator of the Fund, "not later than one year after the date of discovery of damage. The administrator shall prescribe appropriate forms and procedures for such claims." N.J.S.A. 58:10–23.11k. In the event "a party, including a potentially responsible party ... contests the amount or validity of" a claim for reimbursement from the Spill Fund, "the dispute is referred to an arbitrator whose decision may be appealed to the Appellate Division," and the arbitrator's decision will be final unless it was "arbitrary, capricious, or unreasonable." *Lacey Municipal Util. Auth. v. New Jersey Dept. of Envir. Prot., Envir. Claims Admin.*, 369 N.J. Super. 261, 273, 848 A.2d 843 (App.Div.2004). Accordingly, this is an improper forum for a Spill Compensation Fund claim.

Exhibit 23



Zhejiang Jianye Chemical Co.,Ltd

Add: 48th Fuxi Road, Meicheng Town, Jiande City, Zhejiang Province 311604 China

Tel:+86-571-64149210, 64149273

Fax:+86-571-64141300

URL: <http://www.chinaorganicchem.com>

E-mail: trade@chinaorganicchem.com sale@chinaorganicchem.com

CERTIFICATE OF ANALYSIS

DATE:NOV.25,2012

LOT NO.:201209-207-80

Triethylamine Analysis

Property		Specifications	Results
Triethylamine,	wt%	99.5 Min	99.9
Water,	wt%	0.1 Max	0.02
Monoethylamine,	wt%	0.1Max	0.01
Diethylamine,	wt%	0.1Max	0.01
Ethanol,	wt%	0.1Max	N.D
Color ,	APHA	15 Max	10

浙江建业化工股份有限公司
ZHEJIANG JIANYE CHEMICAL CO., LTD.

Sign: 郑丰平

Exhibit 24

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organization, or the World Health Organization.

Concise International Chemical Assessment Document 31

N,N-DIMETHYLFORMAMIDE

Please note that the layout and pagination of this pdf file are not identical to those of the printed CICAD

First draft prepared by

G. Long and M.E. Meek, Environmental Health Directorate, Health Canada, and
M. Lewis, Commercial Chemicals Evaluation Branch, Environment Canada

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



World Health Organization
Geneva, 2001

February 8, 2023

EXHIBIT
AFNAN

006

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

N,N-Dimethylformamide.

(Concise international chemical assessment document ; 31)

1.Dimethylformamide - toxicity 2.Risk assessment 3.Environmental exposure
I.International Programme on Chemical Safety II.Series

ISBN 92 4 153031 6
ISSN 1020-6167

(NLM Classification: QV 633)

The World Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full. Applications and enquiries should be addressed to the Office of Publications, World Health Organization, Geneva, Switzerland, which will be glad to provide the latest information on any changes made to the text, plans for new editions, and reprints and translations already available.

©World Health Organization 2001

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Germany, provided financial support for the printing of this publication.

Printed by Wissenschaftliche Verlagsgesellschaft mbH, D-70009 Stuttgart 10

TABLE OF CONTENTS

FOREWORD	1
1. EXECUTIVE SUMMARY	4
2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES	5
3. ANALYTICAL METHODS	6
3.1 DMF in workplace air	6
3.2 DMF and metabolites in biological media	7
4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE	7
4.1 Natural sources	7
4.2 Anthropogenic sources	7
4.3 Uses	8
5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION	8
5.1 Air	8
5.2 Surface water and sediment	8
5.3 Soil and groundwater	9
5.4 Environmental distribution	10
6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE	10
6.1 Environmental levels	10
6.1.1 Ambient air	10
6.1.2 Surface water and sediment	11
6.1.3 Soil and groundwater	11
6.2 Human exposure	11
6.2.1 Drinking-water	11
6.2.2 Food	11
6.2.3 Multimedia study	11
6.2.4 Exposure of the general population	11
6.2.5 Occupational exposure	12
7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS	12
7.1 Experimental animals	12
7.2 Humans	14
7.2.1 Studies in human volunteers	14
7.2.2 Occupational environment	15
7.2.3 Other relevant data	15
7.3 Interspecies comparisons	15
8. EFFECTS ON LABORATORY MAMMALS AND <i>IN VITRO</i> TEST SYSTEMS	16
8.1 Single exposure	16
8.2 Irritation and sensitization	16
8.3 Short-term exposure	16
8.4 Medium-term exposure	17

Concise International Chemical Assessment Document 31

8.4.1	Inhalation	17
8.4.2	Oral	22
8.5	Long-term exposure and carcinogenicity	22
8.5.1	Inhalation	22
8.5.2	Oral	23
8.5.3	Injection	23
8.6	Genotoxicity and related end-points	23
8.7	Reproductive toxicity	24
8.7.1	Effects on fertility	24
8.7.2	Developmental toxicity	24
8.8	Neurological effects	25
9.	EFFECTS ON HUMANS	25
9.1	Effects on the liver	25
9.2	Cardiac effects	27
9.3	Cancer	28
9.4	Genotoxicity	29
10.	EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD	30
10.1	Aquatic environment	30
10.2	Terrestrial environment	32
11.	EFFECTS EVALUATION	33
11.1	Evaluation of health effects	33
11.1.1	Hazard identification and dose–response assessment	33
11.1.1.1	Effects in humans	33
11.1.1.2	Effects in experimental animals	33
11.1.2	Criteria for setting tolerable concentrations or guidance values	33
11.1.3	Sample risk characterization	34
11.1.4	Uncertainties and degree of confidence in human health risk characterization	35
11.2	Evaluation of environmental effects	35
11.2.1	Terrestrial assessment end-points	35
11.2.2	Sample environmental risk characterization	36
11.2.3	Discussion of uncertainty	36
12.	PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES	37
	REFERENCES	38
	APPENDIX 1 — SOURCE DOCUMENT	47
	APPENDIX 2 — CICAD PEER REVIEW	47
	APPENDIX 3 — CICAD FINAL REVIEW BOARD	48
	APPENDIX 4 — BENCHMARK DOSE CALCULATIONS	49
	INTERNATIONAL CHEMICAL SAFETY CARD	50
	RÉSUMÉ D'ORIENTATION	52
	RESUMEN DE ORIENTACIÓN	54

FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are

provided as guidance only. The reader is referred to EHC 170¹ for advice on the derivation of health-based tolerable intakes and guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

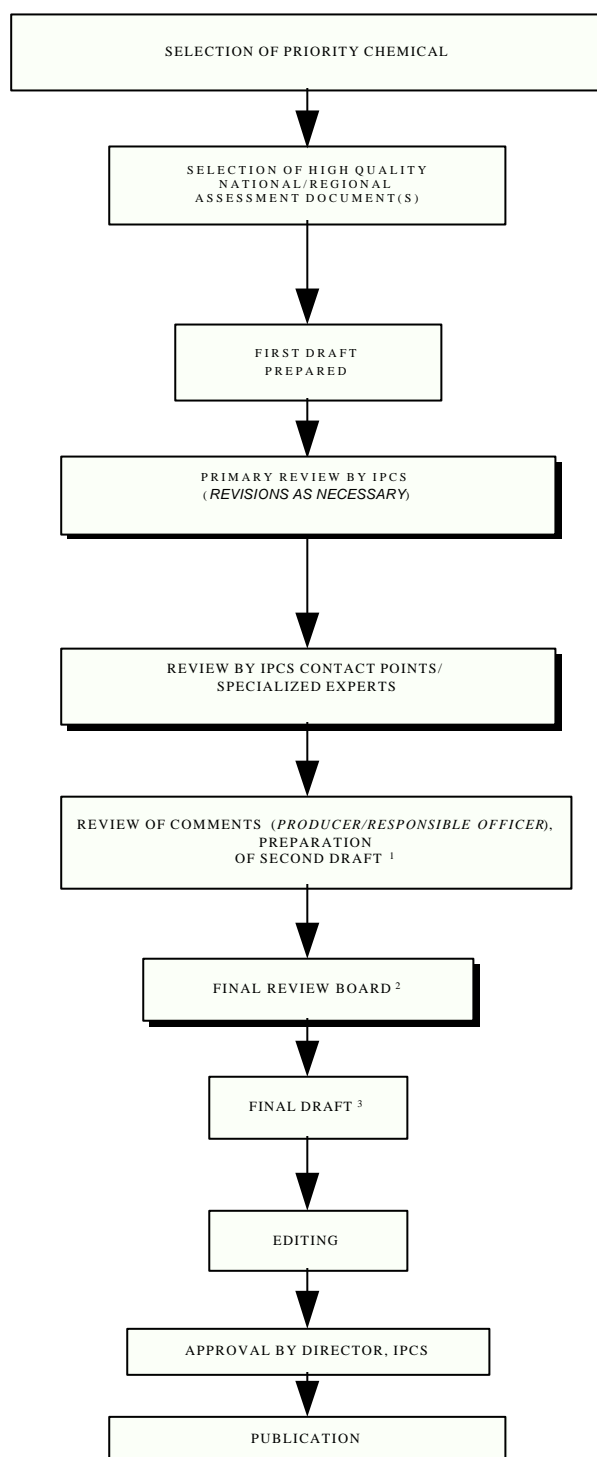
Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, whether a CICAD or an EHC is produced, and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents in order to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft

¹ International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170).

Concise International Chemical Assessment Document 31**CICAD PREPARATION FLOW CHART**

¹ Taking into account the comments from reviewers.

² The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.

³ Includes any revisions requested by the Final Review Board.

is submitted to a Final Review Board together with the reviewers' comments.

A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

Concise International Chemical Assessment Document 31**1. EXECUTIVE SUMMARY**

This CICAD on *N,N*-dimethylformamide (DMF) was prepared jointly by the Environmental Health Directorate of Health Canada and the Commercial Chemicals Evaluation Branch of Environment Canada based on documentation prepared concurrently as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The objective of assessments on Priority Substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Occupational exposure was not addressed in this source document. Data identified as of the end of September 1999 (environmental effects) and February 2000 (human health effects) were considered in this review. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Other reviews that were also consulted include IARC (1999) and BUA (1994). Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Helsinki, Finland, on 26–29 June 2000. Participants at the Final Review Board meeting are presented in Appendix 3. The International Chemical Safety Card (ICSC 0457) for *N,N*-dimethylformamide, produced by the International Programme on Chemical Safety (IPCS, 1999), has also been reproduced in this document.

N,N-Dimethylformamide (CAS No. 68-12-2) is an organic solvent produced in large quantities throughout the world. It is used in the chemical industry as a solvent, an intermediate, and an additive. It is a colourless liquid with a faint amine odour. It is completely miscible with water and most organic solvents and has a relatively low vapour pressure.

When emitted into air, most of the DMF released remains in that compartment, where it is degraded by chemical reactions with hydroxyl radicals. Indirect releases of DMF to air, such as transfers from other environmental media, play only a small role in maintaining levels of DMF in the atmosphere. DMF in air is estimated to be photooxidized over a period of days. However, some atmospheric DMF can reach the aquatic and terrestrial environment, presumably during rain events. When DMF is released into water, it degrades there and does not move into other media. When releases are into soil, most of the DMF remains in the soil — presumably in soil pore water — until it is degraded by biological and chemical reaction. Releases to water or soil are expected to be followed by relatively

rapid biodegradation (half-life 18–36 h). If DMF reaches groundwater, its anaerobic degradation will be slow. The use pattern of DMF is such that exposure of the general population is probably very low.

Since most DMF appears to be released to air in the sample country, and based on the fate of DMF in the ambient environment, biota are expected to be exposed to DMF primarily in air; little exposure to DMF from surface water, soil, or benthic organisms is expected. Based on this, and because of the low toxicity of DMF to a wide range of aquatic and soil organisms, the focus of the environmental risk characterization is terrestrial organisms exposed directly to DMF in ambient air.

DMF is readily absorbed following oral, dermal, or inhalation exposure. Following absorption, DMF is uniformly distributed, metabolized primarily in the liver, and relatively rapidly excreted as metabolites in urine. The major pathway involves the hydroxylation of methyl moieties, resulting in *N*-(hydroxymethyl)-*N*-methylformamide (HMMF), which is the major urinary metabolite in humans and animals. HMMF in turn can decompose to *N*-methylformamide (NMF). In turn, enzymatic *N*-methyl oxidation of NMF can produce *N*-(hydroxymethyl)formamide (HMF), which further degenerates to formamide. An alternative pathway for the metabolism of NMF is oxidation of the formyl group, resulting in *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMCC), which has been identified as a urinary metabolite in rodents and humans. A reactive intermediate, the structure of which has not yet been determined (possibly methyl isocyanate), is formed in this pathway; while direct supporting experimental evidence was not identified, this intermediate is suggested to be the putatively toxic metabolite. Available data indicate that a greater proportion of DMF may be metabolized by the putatively toxic pathway in humans than in experimental animals. There is metabolic interaction between DMF and alcohol, which, though not well understood, may be due, at least in part, to its inhibitory effect on alcohol dehydrogenase.

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with gastrointestinal disturbance, alcohol intolerance, increases in serum hepatic enzymes (aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, and alkaline phosphatase), and histopathological effects and ultrastructural changes (hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex

***N,N*-Dimethylformamide**

lysosomes, pleomorphic mitochondria, and fatty changes with occasional lipogranuloma) being observed.

Based on the limited data available, there is no convincing, consistent evidence of increases in tumours at any site associated with exposure to DMF in the occupational environment. Case reports of testicular cancers have not been confirmed in a cohort and case-control study. There have been no consistent increases in tumours at other sites associated with exposure to DMF.

There is also little consistent, convincing evidence of genotoxicity in populations occupationally exposed to DMF, with results of available studies of exposed workers (to DMF and other compounds) being mixed. The pattern of observations is not consistent with variations in exposure across studies. However, in view of the positive dose-response relationship observed in the one study in which it was investigated, this area may be worthy of additional work, although available data on genotoxicity in experimental systems are overwhelmingly negative.

DMF has low acute toxicity and is slightly to moderately irritating to the eyes and skin. No data were identified regarding the sensitization potential of DMF. In acute and repeated-dose toxicity studies, DMF has been consistently hepatotoxic, inducing effects on the liver at lowest concentrations or doses. The profile of effects includes alterations in hepatic enzymes characteristic of toxicity, increases in liver weight, progressive degenerative histopathological changes and eventually cell death, and increases in serum hepatic enzymes. A dose-response has been observed for these effects in rats and mice following inhalation and oral exposure. Species variation in sensitivity to these effects has been observed, with the order of sensitivity being mice > rats > monkeys.

Although the database for carcinogenicity is limited to two adequately conducted bioassays in rats and mice, there have been no increases in the incidence of tumours following chronic inhalation exposure to DMF. The weight of evidence for genotoxicity is overwhelmingly negative, based on extensive investigation in *in vitro* assays, particularly for gene mutation, and a more limited database *in vivo*.

In studies with laboratory animals, DMF has induced adverse reproductive effects only at concentrations greater than those associated with adverse effects on the liver, following both inhalation and oral exposure. Similarly, in well conducted and reported primarily recent developmental studies, fetotoxic and teratogenic effects

have been consistently observed only at maternally toxic concentrations or doses.

Available data are inadequate as a basis for assessment of the neurological or immunological effects of DMF.

The focus of this CICAD and the sample risk characterization is primarily effects of indirect exposure in the general environment.

Air in the vicinity of point sources appears to be the greatest potential source of exposure of the general population to DMF. Based on the results of epidemiological studies of exposed workers and supporting data from a relatively extensive database of investigations in experimental animals, the liver is the critical target organ for the toxicity of DMF. A tolerable concentration of 0.03 ppm (0.1 mg/m³) has been derived on the basis of increases in serum hepatic enzymes.

Data on the toxicity of DMF to terrestrial vascular plants have not been identified. Effect concentrations for indicators of the potential sensitivities of trees, shrubs, and other plants are high; hence, it is unlikely that terrestrial plants are particularly sensitive to DMF. For other terrestrial organisms, an estimated no-effects value of 15 mg/m³ has been derived based on a critical toxicity value for hepatic toxicity in mice divided by an application factor. Comparison of this value with a conservative estimated exposure value indicates that it is unlikely that DMF causes adverse effects on terrestrial organisms in the sample country.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

N,N-Dimethylformamide (CAS No. 68-12-2) is a colourless liquid at room temperature with a faint amine odour (BUA, 1994). There are many synonyms for this compound, the most common being the acronym DMF. The molecular mass of DMF is 73.09, as calculated from its empirical formula (C₃H₇NO). DMF sold commercially contains trace amounts of methanol, water, formic acid, and dimethylamine (BUA, 1994).

DMF is miscible in all proportions with water and most organic solvents (Syracuse Research Corporation, 1988; Gescher, 1990; BUA, 1994; SRI International, 1994). DMF is also a powerful solvent for a variety of organic, inorganic, and resin products (SRI International, 1994). At temperatures below 100 °C, DMF

Concise International Chemical Assessment Document 31**Table 1: Physical and chemical properties of DMF.**

Property	Value	Reference	Values used in fugacity calculations ^a
Molecular mass	73.09		73.09
Vapour pressure (Pa at 25 °C)	490	Riddick et al. (1986)	490
Solubility (g/m ³)	miscible	BUA (1994)	1.04 × 10 ⁶
Log K _{ow}	! 1.01	Hansch et al. (1995)	! 1.01
Henry's law constant (Pa·m ³ /mol at 25 °C)	0.0345 0.0075	Bobra ^b BUA (1994)	0.034 53 ^c
Density/specific gravity (g/ml at 25 °C)	0.9445	WHO (1991)	
Melting point (°C)	! 60.5	WHO (1991)	! 60.5 °C
Boiling point (°C)	153.5	WHO (1991)	
Half-life in air (h)	approx. 192	estimated from propane	170
Half-life in water (h)	18 36	Dojlido (1979) Ursin (1985)	55
Half-life in soil (h)	assumed to be equivalent to that in water		55
Half-life in sediment (h)	–		170
Half-life in suspended sediment (h)	–		55
Half-life in fish (h)	–		55
Half-life in aerosol (h)	–		5
Odour threshold	0.12–60 mg/m ³	WHO (1991)	

^a Discussed in section 11.1.3, Sample risk characterization.

^b Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

^c Based upon vapour liquid equilibrium data (Hala et al., 1968), as calculated in DMER & AEL (1996).

remains stable in relation to light and oxygen (BUA, 1994). Temperatures in excess of 350 °C are required for DMF to decompose into carbon monoxide and dimethylamine (Farhi et al., 1968).¹

Some important physical and chemical properties of DMF are summarized in Table 1. A vapour pressure of 490 Pa was recommended by Riddick et al. (1986). Because DMF is a miscible compound, it is preferable to determine the Henry's law constant experimentally. However, no experimental data were identified in the literature, and the calculated Henry's law constant of DMF remains uncertain (DMER & AEL, 1996).² The

octanol/water partition coefficient (K_{ow}) was determined by a shake flask experiment (Hansch et al., 1995).

The conversion factor for DMF in air is as follows (WHO, 1991): 1 ppm = 3 mg/m³.

3. ANALYTICAL METHODS

The following information on analytical methods for the determination of DMF in workplace air and biological media has been derived from WHO (1991) and Environment Canada (1999a).

3.1 DMF in workplace air

Colorimetric methods (based on the development of a red colour after the addition of hydroxylamine chloride as alkaline solution) that have often been utilized in the past are not specific (Farhi et al., 1968). Methods of choice more recently are high-performance liquid chromatography (HPLC) or gas chromatography – mass spectrometry (GCMS). Lauwerys et al. (1980)

¹ Also notes from N.J. Bunce, University of Guelph, Guelph, Ontario, to A. Chevrier, Environment Canada, 1 June 1998.

² Also collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

described a simple spectrophotometric method for measuring DMF vapour concentrations. Gas-liquid chromatography (GLC) is now the method of choice (Kimmerle & Eben, 1975a; NIOSH, 1977; Muravieva & Anvaer, 1979; Brugnone et al., 1980; Muravieva, 1983; Stransky, 1986). Detector tubes, certified by the US National Institute for Occupational Safety and Health, or other direct-reading devices calibrated to measure DMF (Krivanek et al., 1978; NIOSH, 1978) can be used. HPLC analysis (Lipski, 1982) can also be used. Mass spectrometric analysis for DMF in expired air has been described by Wilson & Ottley (1981), with a lower limit of detection of 0.5 mg/m³. Figge et al. (1987) reported determination in air involving the enrichment of an organic polymer, thermal desorption of the adsorbed species, and qualitative determination by GCMS. The lower limit of detection was 5 ng/m³. A NIOSH (1994) gas chromatographic (GC) method has an estimated detection limit of 0.05 mg per sample.

3.2 DMF and metabolites in biological media

DMF is extensively absorbed through the skin, its metabolism and kinetics are well known, and urinary metabolites exist that can be accurately measured. As a result, biological monitoring has been extensively used in the assessment of the absorbed amounts in occupationally exposed populations. The metabolite most often analysed is *N*-methylformamide (NMF), and several GC methods exist (Ikeda, 1996). Using nitrogen-sensitive detection, the limit of detection is 0.1 mg/litre.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

4.1 Natural sources

BUA (1994) identified no known natural sources of DMF. However, DMF is a possible product of the photochemical degradation of dimethylamine and trimethylamine (Pellizzari, 1977; Pitts et al., 1978; US EPA, 1986). Both are commonly occurring natural substances and are also used in industrial applications (European Chemicals Bureau, 1996a, 1996b).

4.2 Anthropogenic sources

Identified data on releases are restricted to the country of origin of the source document (Canada). They are presented here in the context of an example of an emissions profile.

In 1996, just over 16 tonnes of DMF were released from various industrial locations in Canada, of which 93% (15 079 kg) were emitted to the atmosphere and the remainder to water (245 kg), wastewater (204 kg), landfill sites (26 kg), or deep-well injection (669 kg) (Environment Canada, 1998). The Canadian market for DMF is quite small, with an estimated domestic consumption in the range of less than 1000 tonnes/year (SRI International, 1994; Environment Canada, 1998). The petrochemical sector was responsible for 84% (12.7 tonnes) of the reported atmospheric releases. Releases from the pharmaceutical industry accounted for 87% (0.212 tonnes) of total releases to water. Total release volumes from Canadian industrial sectors include 13.3 tonnes from the petrochemical sector, 1.2 tonnes from manufacture of pharmaceuticals, 0.7 tonnes from dye and pigment manufacture, 0.6 tonnes from polyvinyl chloride coating operations, 0.1 tonnes from its use as a solvent in pesticide manufacture, 0.07 tonnes from paint/finisher and paint remover manufacture, and 0.09 tonnes from other miscellaneous industrial sectors. For 1996, a reported total quantity of 0.056 tonnes was released (0.023 tonnes to air, 0.033 tonnes to water) by the producer during chemical synthesis of DMF (Environment Canada, 1998). Less than 1 tonne of DMF was released from wastewater treatment facilities and in landfills (Environment Canada, 1998). With a few exceptions, most industries reported little to no seasonal variation in releases (Environment Canada, 1998).

In the USA, between 23 and 47 million kilograms of DMF were produced in 1990 (US EPA, 1997).

World production of DMF is estimated to be 125 000 tonnes (Marsella, 1994).

The total consumption of DMF in Western Europe in 1989 was reported to be 55 000 tonnes (BUA, 1994). The production capacity was estimated to be 60 000 and 19 000 tonnes in the former Federal Republic of Germany and German Democratic Republic, respectively, 16 000 tonnes in Belgium, 15 000 tonnes in England, and 5000 tonnes in Spain (BUA, 1994).

Although small accidental releases (e.g., leakage of a storage tank or spill from a barrel) may remain unreported, available information suggests that spills of DMF during use, storage, or transport are not a significant route of entry to the environment (Environment Canada, 1999a).

The quantity of DMF in landfill sites should be small. The total quantity of DMF used in formulation of products (other than pesticides) appears to be small in comparison to its use as a manufacturing aid, cleaner, or degreaser (Environment Canada, 1998). As such,

Concise International Chemical Assessment Document 31

consumer products deposited in landfill sites should contain little or no DMF. The industrial DMF deposited directly in landfill sites consists only of residues remaining after incineration (Environment Canada, 1998).

4.3 Uses

DMF is used commercially as a solvent in vinyl resins, adhesives, pesticide formulations, and epoxy formulations; for purification and/or separation of acetylene, 1,3-butadiene, acid gases, and aliphatic hydrocarbons; and in the production of polyacrylic or cellulose triacetate fibres and pharmaceuticals (WHO, 1991; IARC, 1999). DMF is also used in the production of polyurethane resin for synthetic leather (Fiorito et al., 1997).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION**5.1 Air**

The atmospheric pathway is particularly important in determining exposure to DMF. This is due to the fact that industrial releases of DMF into air appear to be considerably larger than releases to other environmental media (BUA, 1994; Environment Canada, 1998).

Because of the complete miscibility of DMF in water, atmospheric DMF may be transported from air into surface water or soil pore water during rain events (DMER & AEL, 1996).¹ Atmospheric DMF should be present in the vapour phase and therefore should be readily available for leaching out by rainfall (US EPA, 1986).² Although the efficiency and rate of washout are unknown, precipitation events (i.e., rain, snow, fog) likely shorten the residence time of DMF in the atmosphere. As water has an atmospheric half-life of approximately 4 days at Canadian latitudes, this can be considered the minimum atmospheric half-life of DMF in relation to precipitation.¹

Chemical degradation of DMF in air is likely due to reaction with hydroxyl radicals (Hayon et al., 1970). The

possibility of photochemical decomposition (i.e., direct photolysis) of DMF is extremely small (Grasselli, 1973; Scott, 1998). Other chemical degradation processes — for example, reaction with nitrate radicals — are not known to significantly affect the fate of DMF in air.

The reaction rate constant (k_{OH}) for the formamide functional group is unknown. However, the degradation half-life of DMF can be roughly estimated by comparing DMF with other compounds in terms of their relative atmospheric reactivity.

Based on experiments in chambers, reactivity for DMF relative to propane is low (Sickles et al., 1980). The k_{OH} of propane is 1.2×10^{-12} cm³/molecule per second (Finlayson-Pitts & Pitts, 1986). Using the global average hydroxyl radical concentration of 7.7×10^5 molecules/cm³ (Prinn et al., 1987) and the calculation method proposed by Atkinson (1988), the half-life of propane is estimated at approximately 8 days.

Although the degradation half-life of DMF in air cannot be estimated with certainty, the available evidence therefore suggests that the half-life is at least 8 days (192 h). The mean half-life used for fugacity-based fate modelling was 170 h, as it is frequently used to represent a half-life range of 100–300 h (DMER & AEL, 1996). This half-life may be underestimated; however, sensitivity analysis on the fugacity-based results indicates that percent partitioning estimates are not sensitive to this parameter, but estimated concentrations are affected.³

5.2 Surface water and sediment

Once released into surface water, DMF is unlikely to transfer to sediments, biota, or the atmosphere. With a K_{ow} of 1.01 (Hansch et al., 1995), DMF remains in the dissolved form and is not expected to adsorb to the organic fraction of sediments or suspended organic matter. This K_{ow} also suggests that DMF does not concentrate in aquatic organisms (BUA, 1994); indeed, no bioaccumulation was observed in carp during an 8-week bioaccumulation test (Sasaki, 1978). With a Henry's law constant of 0.0345 Pa·m³/mol, volatilization from water is expected to be slight (BUA, 1994).³

The overall rate of chemical degradation is expected to be very slow in surface water.

¹ Also letter from D.R. Hastie, York University, Toronto, Ontario, to P. Doyle, Environment Canada, 1998.

² Also technical note from N.J. Bunce, University of Guelph, Guelph, Ontario, to B. Scott, Environment Canada, dated 10 February 1998.

³ Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

N,N-Dimethylformamide

Photochemical decomposition is unlikely in water (Grasselli, 1973; US EPA, 1986). The photooxidation half-life of DMF in water was estimated experimentally at 50 days and would be even longer in the natural environment where other compounds compete for reaction with hydroxyl radicals (Hayon et al., 1970). The rate of hydrolysis of amides like DMF at normal temperatures in laboratory studies is extremely slow, even under strong acid or base conditions (Fersht & Requena, 1971; Eberling, 1980). The low temperature (generally less than 20 °C) and near-neutral pH of natural surface water therefore limit and almost preclude the hydrolysis of DMF under normal environmental conditions (Frost & Pearson, 1962; Langlois & Broche, 1964; Scott, 1998).

Biodegradation appears to be the primary degradation process in surface water. Under experimental conditions, DMF was degraded, either aerobically or anaerobically, by various microorganisms and algae in activated sludges, over a wide range of concentrations (Hamm, 1972; Begert, 1974; Dojlido, 1979). Intermediate biodegradation products include formic acid and dimethylamine, which further degrade to ammonia, carbon dioxide, and water (Dojlido, 1979; Scott, 1998). In some studies, acclimation periods of up to 16 days preceded quantitative degradation (Chudoba et al., 1969; Gubser, 1969). Extended adaptation under specific experimental conditions may also account for negative degradation results observed in a few studies with incubation times \geq 14 days (Kawasaki, 1980; CITI, 1992). Limited degradation was reported in seawater (range 1–42%) (Ursin, 1985), and no degradation was found after 8 weeks' incubation under anaerobic conditions (Shelton & Tiedje, 1981).

Biodegradation of DMF in receiving surface waters is unlikely to be affected by the inherent toxicity of DMF and its biodegradation products. Concentrations above 500 mg/litre in effluent reduced the efficiency of treatment systems using activated sludge (Thonke & Dittmann, 1966; Nakajima, 1970; Hamm, 1972; Begert, 1974; Carter & Young, 1983). However, even with continuous releases, such high concentrations of DMF are not anticipated in natural waters.

In a river die-away test, an initial concentration of 30 mg DMF/litre completely disappeared within 3 and 6 days from unacclimated and acclimated water, respectively (Dojlido, 1979). The mineralization rate of DMF in seawater was less than 3% in 24 h for initial concentrations of 10 µg/litre and 100 µg/litre. However, 20% was mineralized in 24 h at a concentration of 0.1 µg/litre (Ursin, 1985). A half-life of 55 h was used for water in the fugacity-based fate modelling described in

section 5.4 (DMER & AEL, 1996).^{1,2} No information is available on the half-life of DMF in sediments. DMER & AEL (1996) recommend a half-life in sediment of 170 h based on the assumption that reactivity in sediment is slower than in soil.

5.3 Soil and groundwater

Fugacity-based fate modelling and the miscibility of DMF indicate that some of the DMF released into the atmosphere can reach the ground, in part, at least, through rainfall (DMER & AEL, 1996).^{1,2} Once in soils, DMF will be degraded by chemical and biological processes or leached into groundwater.

As rain fills the available pore space in soils, DMF is incorporated into the pore water. With an octanol/water partition coefficient of $\log K_{ow}$ 1.01 (Hansch et al., 1995), DMF will not tend to adsorb to humic material. Weak bonds with the mineral phase are possible but likely insignificant because of the high solubility of DMF.³

Biological degradation and, to a lesser extent, chemical processes operating in surface water would also likely affect DMF contained in soil pore water (Scott, 1998). As for surface water, biodegradation should therefore be the primary breakdown mechanism in soils. A soil bacterial culture acclimated to small amounts of petroleum and petroleum products degraded DMF under aerobic conditions within 18 h (Romadina, 1975), indicating a soil biodegradation half-life similar to the one observed in water. A somewhat longer conservative half-life of 55 h was used in fugacity-based fate modelling (DMER & AEL, 1996).^{1,2}

The miscibility of DMF and its low Henry's law constant indicate limited volatilization from moist soils (BUA, 1994). However, DMF will be efficiently removed from soils by leaching into groundwater, likely at the same speed as water percolates through the soil.⁴ This is

¹ Also technical note sent from R. Beauchamp, Health Canada, to A. Chevrier, Environment Canada, 1998.

² Also collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

³ Letter from K. Bolton, University of Toronto, Toronto, Ontario, to A. Chevrier, Environment Canada, dated 8 June 1998.

⁴ Technical note from S. Lesage to B. Elliott, Environment Canada, dated 26 November 1997.

Concise International Chemical Assessment Document 31

supported by a calculated organic carbon/water partition coefficient (K_{oc}) of 7 (Howard, 1993) and a soil sorption coefficient (K_{om}) of about 50, estimated from quantitative structure–activity relationships (Sabljic, 1984; US EPA, 1986), which both indicate that DMF is mobile in soils. If it reaches groundwater, DMF will be slowly degraded anaerobically (Scott, 1998).¹

5.4 Environmental distribution

Fugacity modelling was conducted to provide an overview of key reaction, intercompartment, and advection (movement out of a system) pathways for DMF and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity modelling) was run using the methods developed by Mackay (1991) and Mackay & Paterson (1991). Assumptions, input parameters, and results are summarized in Environment Canada (1999a) and presented in detail in DMER & AEL (1996) and by Beauchamp² and Bobra.³ Modelling predictions do not reflect actual expected concentrations in the environment but rather indicate the broad characteristics of the fate of the substance in the environment and its general distribution among the media.

Modelling results identify air as an important exposure medium. If DMF is emitted into air, fugacity modelling predicts that 61% of the chemical will be present in air, 32% in soil, and only 7% in water. These results suggest that most of the DMF released into air will remain in that compartment, where it will be degraded by chemical reactions. They also indicate that some atmospheric DMF can reach the aquatic and terrestrial environment — presumably in rain and runoff (Scott, 1998).⁴ However, the quantity of DMF available for entrainment in rain and runoff is limited by degradation in the atmosphere.

Fugacity modelling also indicates that when DMF is continuously discharged into either water or soil, most of it can be expected to be present in the receiving medium. For example, if it is released into water, 99% of the DMF is likely to be present in the water, and subsequent transport into sediment or bioconcentration in biota is not likely to be significant. When releases are into soil, 94% of the material remains in the soil — presumably in soil pore water (Scott, 1998). Therefore, indirect releases of DMF to air, such as transfers from other environmental media, play only a small role in maintaining levels of DMF in the atmosphere.

It is important to note that fugacity-based partitioning estimates are significantly influenced by input parameters such as the Henry's law constant, which, in this case, is highly uncertain. Therefore, the above partitioning estimates are also uncertain.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

6.1.1 Ambient air

Concentrations of DMF in stack emissions of two Canadian industries were less than 7.5 mg/m³ (Environment Canada, 1998, 1999b). Data on concentrations in ambient air around these sources are not available.

In Lowell, Massachusetts, USA (Amster et al., 1983), DMF was detected in the air over an abandoned chemical waste reclamation plant (0.007 mg/m³), a neighbouring industry (>0.15 mg/m³), and a residential area (0.024 mg/m³). Ambient air samples collected in the northeastern USA in 1983 ranged from less than 0.000 02 to 0.0138 mg DMF/m³ (Kelly et al., 1993, 1994). In samples taken in 1983, levels of DMF were generally less than 0.02 mg/m³ at a hazardous waste site in unsettled wind conditions, possibly as high as 9 mg/m³ at nearby industrial sites, and less than 0.02 mg/m³ in adjoining residential areas (Clay & Spittler, 1983).

A range of 0.000 11 – 0.0011 mg/m³ was reported in Japan in 1991, but specific locations and proximity to sources were not provided (Environment Agency Japan, 1996). In Germany, a concentration of 0.005 µg DMF/m³ was detected in air (Figge et al., 1987).

¹ Technical note from S. Lesage to B. Elliott, Environment Canada, dated 26 November 1997.

² Technical note sent from R. Beauchamp, Health Canada, to A. Chevrier, Environment Canada, 1998.

³ Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

⁴ Also letter from S. Lei, Atomic Energy Control Board of Canada, to A. Chevrier, Environment Canada, dated 11 June 1998.

N,N-Dimethylformamide

6.1.2 Surface water and sediment

DMF was detected (detection limit 0.002 mg/litre) in only 1 of 204 surface water samples collected between August 1975 and September 1976 from 14 heavily industrialized river basins in the USA (Ewing et al., 1977). The Environment Agency Japan (1996) reported concentrations between 0.0001 and 0.0066 mg/litre in 18 out of 48 water samples taken in 1991. In addition, in 24 water samples collected in 1978, levels were below the detection limits of 0.01–0.05 mg/litre (Environment Agency Japan, 1985). The proximity of these measurements to industrial sources is not known.

In Canada, monitoring data are available for effluents at one southern Ontario location, which released less than ~0.03 tonnes into surface water in 1996 (Environment Canada, 1998). The facility reported a range of <1–10 mg DMF/litre in effluents, but has since established a wastewater treatment plant, which reduced its effluent concentrations to non-detectable levels (detection limit 0.5 mg/litre). DMF was detected in 1 of 63 industrial effluents in the USA at a detection limit of approximately 0.01 mg/litre (Perry et al., 1979). The US Environmental Protection Agency (EPA)¹ also cited an effluent concentration of 0.005 mg/litre at a sewage treatment plant in 1975.

The properties of DMF and fugacity modelling indicate negligible accumulation of DMF in sediments (BUA, 1994; Hansch et al., 1995; DMER & AEL, 1996).^{2,3} However, concentrations of 0.03–0.11 mg/kg were reported in sediments (9 out of 48 samples) in Japan (Environment Agency Japan, 1996). No information was provided on proximity to sources of DMF, sediment characteristics, or hydrological regimes. In addition, because information on sampling and analytical methods was not provided, the quality of these data cannot be assessed. In 24 sediment samples collected in 1978 at unspecified locations in Japan, levels were below the detection limits of 0.1–0.3 mg/kg (Environment Agency Japan, 1985).

¹ Group STORET search on DMF, obtained from J. Boyd, US EPA (storet@epamail.eap.gov), on 30 July 1999.

² Also technical note sent from R. Beauchamp, Health Canada, to A. Chevrier, Environment Canada, 1998.

³ Also collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

6.1.3 Soil and groundwater

In 3 of 23 groundwater samples collected in the USA, concentrations ranged from 0.05 to 0.2 mg/litre, with an average value of 0.117 mg/litre (Syracuse Research Corporation, 1988).¹

6.2 Human exposure**6.2.1 Drinking-water**

Although DMF was listed as a contaminant in a survey of drinking-water in the USA, quantitative data were not reported (Howard, 1993).

6.2.2 Food

Data on concentrations of DMF in foods were not identified.

6.2.3 Multimedia study

A Health Canada-sponsored multimedia exposure study for DMF and other volatile organic compounds was conducted in 50 homes in the Greater Toronto Area in Ontario, Nova Scotia, and Alberta (Conor Pacific Environmental, 1998). DMF was not detected in indoor air samples from the 50 residences (detection limit 3.4 µg/m³). It was also not detected in tap water samples, although the limit of detection was high (0.34 µg/ml). DMF was not recovered reproducibly in composite food or beverage samples in this study.

6.2.4 Exposure of the general population

Identified data on concentrations of DMF in environmental media in Canada were insufficient to allow estimates of population exposure to be developed; for water, either quantitative data on concentrations are unreliable⁴ or DMF has not been detected, using analytical methodology with poor sensitivity (Conor Pacific Environmental, 1998).

Non-pesticidal use of DMF in Canada is small and restricted primarily to industrial applications. Most DMF released into the environment in Canada during such use is emitted to air. Most DMF remains in the medium of release prior to degradation. Therefore, the greatest potential for exposure of the general population to DMF

⁴ Technical notes regarding data from Environmental Monitoring and Reporting Branch, Ontario Ministry of Environment and Energy, sent to J. Sealy, Health Canada, 1996.

Concise International Chemical Assessment Document 31

from non-pesticidal sources is in air in the vicinity of industrial point sources.

Based upon dispersion modelling of releases in Canada from the highest emitter over a 1-km radius, 100 m in height, the estimated ambient concentration is $110 \mu\text{g}/\text{m}^3$. Although this value is comparable to levels measured under similar conditions in other countries, it is based on very conservative assumptions; taking into account more likely conditions, including some loss due to advection, estimated concentrations would be 10- to 100-fold less (i.e., 11 or $1.1 \mu\text{g}/\text{m}^3$).

Based on lack of detection in a multimedia study, levels of DMF in indoor air of 50 homes in Canada were less than $3.4 \mu\text{g}/\text{m}^3$ (Conor Pacific Environmental, 1998).

6.2.5 Occupational exposure

Occupational exposure to DMF may occur in the production of the chemical itself, other organic chemicals, resins, fibres, coatings, inks, and adhesives (IARC, 1999). Exposure may also occur during use of these coatings, inks, and adhesives in the synthetic leather industry, in the tanning industry, and as a solvent in the repair of aircraft (Ducatman et al., 1986; IARC, 1989).

Based on data from the National Exposure Data Base, maintained by the United Kingdom Health and Safety Executive, concentrations of DMF in workplace air in the manufacture of textiles ranged from 0.1 to 10.5 ppm (0.3 to $7.5 \text{ mg}/\text{m}^3$) in 16 facilities.¹ For the six facilities where data were reported, the 8-h time-weighted average (TWA) concentration ranged from 4 to 12.4 ppm (12 to $37.2 \text{ mg}/\text{m}^3$). At six facilities where plastic was manufactured, concentrations ranged from 0.1 to 0.7 ppm (0.3 to $2.1 \text{ mg}/\text{m}^3$). At 11 facilities for plastics processing, the range of concentrations was from 4 to 44 ppm (12 to $132 \text{ mg}/\text{m}^3$); the range of 8-h threshold limit values (TLVs) at six of the facilities was 5–38 ppm (15– $114 \text{ mg}/\text{m}^3$).

In the USA between 1981 and 1983, approximately 125 000 workers were potentially exposed to DMF, with 13 000 workers potentially exposed for more than 20 h/week (NIOSH, 1983).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Available data indicate that DMF is readily absorbed following oral, dermal, and inhalation exposure in both humans and animals. The rate of dermal absorption was estimated to be $57 \text{ mg}/\text{cm}^2$ per 8 h in a rat tail model. DMF is metabolized primarily in the liver and is relatively rapidly excreted as metabolites in urine, primarily as *N*-(hydroxymethyl)-*N*-methylformamide (HMMF).

7.1 Experimental animals

The major metabolic pathway for DMF in mammalian species is oxidation by the cytochrome P-450-dependent mixed-function oxidase system to HMMF (Figure 1). This can generate NMF and formaldehyde (see review by Gescher, 1993). Further cytochrome P-450-mediated oxidation of NMF and/or HMMF results in the formation of *S*-(*N*-methylcarbamoyl)glutathione (SMG), the conjugate of the presumed reactive (toxic) intermediate, methyl isocyanate, excreted *in vivo* as *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMCC). Results of studies with liver microsomes from acetone-treated rats (Mráz et al., 1993; Chieli et al., 1995) and mice (Chieli et al., 1995) and with reconstituted enzyme systems indicate that cytochrome P-450 2E1 mediates the metabolism of DMF to HMMF and, subsequently, to the proposed reactive intermediate, methyl isocyanate.

The most informative of the toxicokinetic and metabolic studies relevant to consideration of inter-species and dose-related variations in toxicokinetics and metabolism include investigations following oral administration to rats and inhalation exposure of rats, mice, and monkeys.²

In female Sprague-Dawley rats administered a single oral dose of 100 mg ^{14}C -labelled DMF/kg body weight on day 12 or 18 of pregnancy, 60–70% of the radioactivity was excreted in urine and 3–4% in faeces at 48 h (Saillenfait et al., 1997). Approximately 4% of the dose was present in the liver at 0.5 h after dosing at both gestation times, with 8 and 13% in the gastrointestinal tract (stomach and intestine) and 0.7 and 0.8% in

¹ Data retrieval by J. Tickner from National Exposure Data Base, Health and Safety Executive (hse.gsi.gov.uk), 2000.

² In early studies, HMMF was not reported, since it degraded to NMF thermolytically in GLC conditions; hence, in early investigations, $\text{NMF} = \text{HMMF} + \text{NMF}$. HMMF is stable in aqueous solutions of neutral or mildly acidic pH but undergoes thermal decomposition to NMF during routine GC analysis. Therefore, it was first identified as NMF.

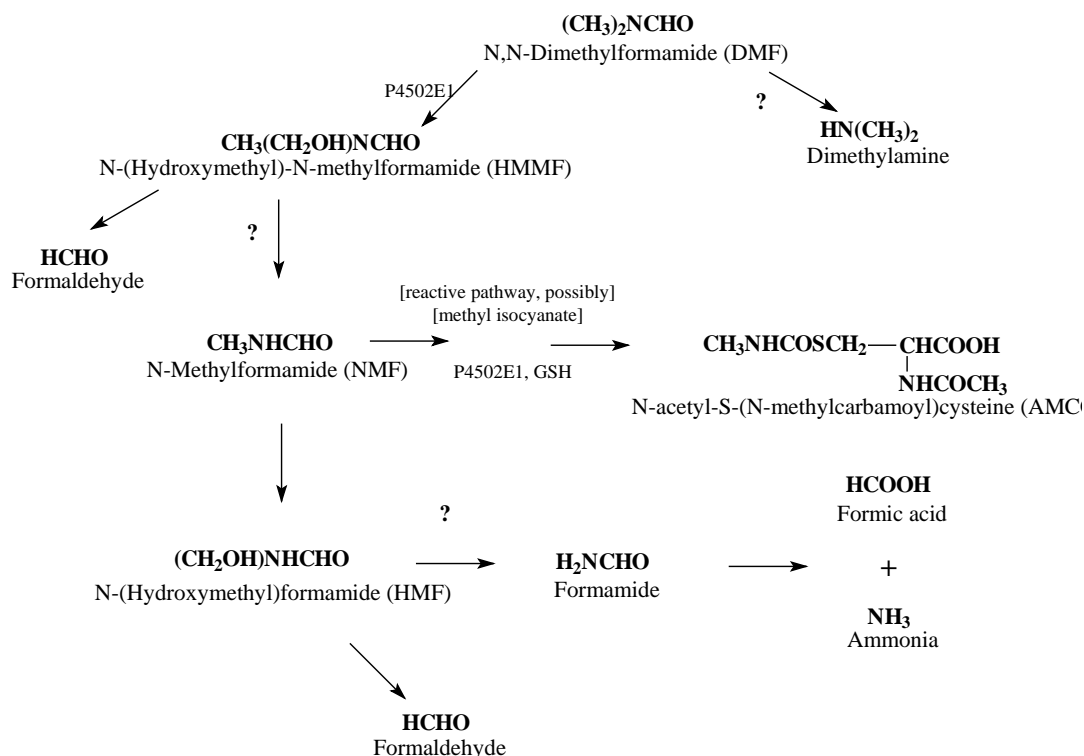
N,N-Dimethylformamide

Fig. 1. Biotransformation of DMF (adapted from WHO, 1991; Gescher, 1993).

the kidneys, respectively. Plasma radioactivity was relatively constant from 0.5 to 4 h after dosing (approximately 0.4–0.5% of the dose) but declined rapidly thereafter. By 48 h, only the liver (0.5 and 0.6%) and intestine (0.2 and 0.3%) retained any significant activity. In animals exposed on day 12 of gestation, approximately 1.5% of the dose was present in the uterus, placenta, embryo, and amniotic fluid at between 0.5 and 4 h, which rapidly declined to less than 0.1% at 24 h. In rats exposed on day 18 of gestation, fetal tissues accounted for 6% of the administered dose. HPLC analysis performed at intervals from 1 to 24 h indicated that unchanged DMF and metabolites were readily transferred to the embryonic and fetal tissues, where levels were generally equal to those in maternal plasma. The parent compound accounted for most of the radioactivity until 4–8 h and then decreased.

Levels of parent compound and metabolites were determined in the plasma, amniotic fluid, placenta, and embryo in this investigation. Unchanged DMF initially accounted for the major proportion of radiolabelled carbon in the plasma or tissues, 61–77% for the first 4 h and 73–93% for the first 8 h after treatment on days 12 and 18, respectively. The decline in DMF levels corresponded with an increase in the levels of HMMF and NMF. HMMF accounted for 40–47% of ^{14}C at 8 h (day 12) and for 41–55% at 16 h (day 18). The equivalent figures for NMF were 9–13% and 16–18%, respectively. The amounts of AMCC and formamide in plasma or tissues were <4% of total radioactivity at all time points (Saillenfait et al., 1997). Other investigators have reported that DMF also crosses the placenta of pregnant rats after inhalation exposure (Sheveleva et al., 1977; Shumilina, 1991).

Concise International Chemical Assessment Document 31

In another of the few recent investigations, levels of DMF, NMF, and HMMF were determined in the blood and urine of B6C3F1 mice and Crl:CD BR rats exposed to 10, 250, or 500 ppm (30, 750, or 1500 mg/m³) for either single exposures of 1, 3, or 6 h or for 6 h/day, 5 days/week, for 2 weeks (Hundley et al., 1993a). The values for area under the plasma concentration curve (AUC) for DMF increased disproportionately in comparison with exposure, following single 6-h exposures to 250 and 500 ppm (750 and 1500 mg/m³) (8- and 28-fold for rats and mice, respectively), while levels of NMF in the blood did not increase, which the authors considered to be indicative of saturation of metabolism of DMF. In contrast, multiple exposures increased the capacity of both rats and mice to metabolize DMF; repeated exposures to 500 ppm (1500 mg/m³) resulted in a 3- and 18-fold reduction in AUC values for rats and mice, respectively. Peak plasma levels for NMF were elevated. HMMF represented over 90% of the total of DMF and determined metabolites.

In a similar investigation, DMF, NMF, and HMMF in blood and urine were determined in male and female cynomolgus monkeys exposed to 30, 100, or 500 ppm (90, 300, or 1500 mg/m³) for 6 h/day, 5 days/week, for 13 weeks (Hundley et al., 1993b). The values for the AUC increased disproportionally between 100 and 500 ppm (300 and 1500 mg/m³) (19- to 37-fold in males and 35- to 54-fold in females), data consistent with saturation of metabolism. However, there was no corresponding decrease in NMF levels; rather, they increased proportionally with increases in exposure concentrations. For each concentration, AUC values, peak plasma concentration, and plasma half-lives were consistent throughout the duration of exposure. HMMF was the main urinary metabolite (56–95%), regardless of exposure level or duration of exposure. DMF was not readily excreted in the urine, and NMF was more prevalent in plasma than in urine, suggesting that it was metabolized to compounds not determined in the study.

In comparative analyses of the two studies, the authors indicated that toxicokinetic differences may, in part, contribute to the observed species differences in toxicity. The AUC values and peak plasma levels for DMF for rats and mice following a single 500 ppm (1500 mg/m³) exposure are substantially greater than the respective values in monkeys following a similar exposure. Whereas repeated exposures to 500 ppm (1500 mg/m³) in rats and mice enhanced metabolism, as indicated by diminished AUC values for DMF and increased plasma concentrations of NMF, this effect was not clearly demonstrated in monkeys.

Results of the more recent study in rats were qualitatively similar to earlier investigations in which plasma DMF and “NMF” levels were determined in the plasma of rats exposed to DMF by inhalation for single 3- or 6-h exposures (Kimmerle & Eben, 1975a; Lundberg et al., 1983). Results of several of these earlier studies were also suggestive that at very high concentrations, DMF inhibits its own biotransformation. For example, 3 h following a single 4-h inhalation exposure of rats to 1690 or 6700 mg/m³, levels of NMF in blood were lower in the higher exposure group (Lundberg et al., 1983). Similarly, Kimmerle & Eben (1975a) reported lower concentrations of NMF in the blood of rats exposed to 6015 mg/m³ for 3 h than in rats exposed to 513 mg/m³ for 6 h.

In a number of early studies, the effects of co-administration of ethanol on blood concentrations of DMF, NMF, ethanol, and acetaldehyde were investigated. Although there were variations in results depending on dose, time interval between administration of DMF and ethanol, and routes of exposure, there were increases in concentrations of DMF, NMF, ethanol, or acetaldehyde in blood upon co-exposure. These results may be attributable to inhibition by DMF of the activity of alcohol dehydrogenase observed both *in vitro* and *in vivo* (Eben & Kimmerle, 1976; Hanasono et al., 1977; Sharkawi, 1979) and of aldehyde dehydrogenase observed *in vivo* (Elovaara et al., 1983).

7.2 Humans

7.2.1 Studies in human volunteers

There were a number of early investigations in which the parent compound and some metabolites (not including that of the putatively toxic pathway) in blood and urine were determined in volunteers following short-term exposure to DMF (26 or 87 ppm [78 or 261 mg/m³] for 4 h or 4 h/day for 5 days) (Kimmerle & Eben, 1975b). Results of these investigations indicated that DMF was rapidly excreted (the majority in 24 h), primarily as HMMF. Results of an additional early study in volunteers indicated that co-exposure to ethanol had a “slight influence” on the metabolism of DMF in volunteers receiving 19 g of ethanol 10 min prior to exposure to 82 ppm (246 mg/m³) DMF for 2 h, based on lower concentrations of NMF in blood upon co-exposure. Contrary to the results in animals, there were no significant differences in the blood levels of ethanol and acetaldehyde upon co-exposure, which the authors attributed to the relatively low concentrations of DMF (Eben & Kimmerle, 1976).

In a recent study in which the product of the putatively toxic pathway of metabolism (AMCC) was determined, 10 volunteers were exposed to 10, 30, or 60 mg DMF/m³, for either single 8-h exposures or five daily exposures of 30 mg/m³ (Mráz & Nohová, 1992a, 1992b). Urine was collected for 5 days and analysed for DMF, HMMF, HMF, and AMCC. In a separate protocol, three volunteers ingested 20 mg AMCC dissolved in water, and metabolites were determined for a period of 8 h after exposure. After single exposure to 30 mg/m³, the proportions of metabolites eliminated in the urine were 0.3% parent compound, 22.3% HMMF, 13.2% HMF, and 13.4% AMCC. The half-times of excretion for these various metabolites were approximately 2, 4, 7, and 23 h, respectively. In contrast to this slow elimination after exposure to DMF, AMCC was rapidly eliminated after ingestion of AMCC, with a half-time of 1 h. These results were considered to be consistent with rate-limiting reversible protein binding of a reactive metabolic intermediate of DMF, possibly methyl isocyanate. Following repeated exposures, AMCC accumulated in urine. Although quantitative data were not presented, urinary elimination 16 h following the fifth exposure was approximately 14% HMMF, 32% HMF, and 54% AMCC.

7.2.2 Occupational environment

Exposure in the occupational environment may occur through both the dermal and inhalation routes. Lauwerys et al. (1980) reported that dermal absorption was more important than inhalation in the overall exposure, in the absence of personal protective devices.

There have been a number of reports of levels of DMF and metabolites in the blood and/or urine of workers. With the exception of more recent studies involving personal air sampling (Wrbitzky & Angerer, 1998),¹ few provide reliable quantitative data on relationship with exposure, though still not accounting for additional dermal exposure. Results of such studies have confirmed, however, the presence of AMCC (the product of the putatively toxic metabolic pathway) in the urine of workers.

Wrbitzky & Angerer (1998) noted a weak association between the concentration of DMF in workplace air and urinary concentration of NMF. Kawai et al. (1992) considered the relationship to be linear. In 116 workers exposed to TWA concentrations of 0.2, 0.4, 0.6, 3.9, or

9.1 ppm (0.6, 1.2, 1.8, 11.7, or 27.3 mg/m³), the corresponding concentrations of NMF in urine were 0.7, 0.9, 2.6, 7.8, and 19.7 mg/litre.

Mráz et al. (1989) reported the detection of HMMF in urine samples from 12 DMF-exposed workers (extent of exposure not specified). Casal Lareo & Perbellini (1995) reported that AMCC accumulated throughout the work week in the urine of workers exposed to approximately 3–8 ppm (9–24 mg/m³). Sakai et al. (1995) reported that levels of urinary AMCC remained constant over consecutive work days and increased after the end of exposure, with the peak concentration observed at 16–40 h after the end of exposure. Kafferlein¹ reported that urinary NMF concentrations were highest in post-shift samples, with a median half-time of 5.1 h. Concentrations of urinary AMCC reached a steady state 2 days after the beginning of exposure, with a half-time greater than 16 h.

7.2.3 Other relevant data

Angerer et al. (1998) reported that haemoglobin from individuals occupationally exposed to DMF contained *N*-carbamoylated valine residues derived from methyl isocyanate, the likely precursor of AMCC. The metabolism of DMF to HMMF by human liver microsomes *in vitro* has also been demonstrated. The addition of an antibody against rat liver cytochrome P-450 2E1 to the incubation mixture strongly inhibited DMF metabolism (Mráz et al., 1993).

7.3 Interspecies comparisons

In one of the few identified studies in which the product of the putatively toxic metabolic pathway (i.e., AMCC) was determined in animal species, Mráz et al. (1989) reported data on metabolites of DMF (DMF, HMMF, “HMF,” AMCC) in 72-h urine samples following intraperitoneal administration of 0.1, 0.7, or 7 mmol/kg body weight to mice, rats, and hamsters. In addition, 10 healthy volunteers (5 males, 5 females) were exposed for 8 h to 20 ppm (60 mg/m³). (The mean of the amount of DMF absorbed via the lung was reported to be half of the lowest dose administered in rodents.) Urine was collected and analysed for the same metabolites at 2- to 8-h intervals for 8 h for 4–5 days. The proportion of the total metabolites eliminated as AMCC was greatest in the rat (1.7–5.2%) and less in the hamster (1.5–1.9%) and mouse (1.1–1.6%). In rats exposed to the highest dose, excretion of DMF metabolites (including AMCC) was delayed. There was no clear dose-related variation in proportion of the metabolites determined excreted as AMCC in the animal species. In humans, a greater proportion of the absorbed dose (14.5%) following

¹ Also written comments provided by H. Kafferlein, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nuremberg, Germany, 2000.

Concise International Chemical Assessment Document 31

inhalation was present as AMCC in the urine. Absorption through the skin was not taken into account.

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

Following oral, dermal, inhalation, or parenteral administration, the acute toxicity of DMF in a number of species is low. Lethal doses are generally in the g/kg body weight range for oral, dermal, and parenteral routes and in the g/m³ range for inhalation exposure. Clinical signs following acute exposure include general depression, anaesthesia, loss of appetite, loss of body weight, tremors, laboured breathing, convulsions, haemorrhage at nose and mouth, liver injury, and coma preceding death. Where protocols included histopathological examination, damage was observed primarily in the liver (WHO, 1991). In the rat, oral LD₅₀s range from 3000 to 7170 mg/kg body weight, dermal LD₅₀s range from 5000 to >11 520 mg/kg body weight, and inhalation LC₅₀s range from 9432 to 15 000 mg/m³ (WHO, 1991).

8.2 Irritation and sensitization

Standard tests for dermal irritation by DMF have not been identified, and data on its sensitization potential are conflicting. Hence, only limited conclusions can be drawn concerning the potential of DMF to induce these effects.

IARC (1999), WHO (1991), and Kennedy (1986) reviewed the effects of DMF on the skin and eyes and reported only mild to moderate effects. A single application of neat DMF to the shaved skin of mice at 1–5 g/kg body weight (precise exposure conditions not specified) produced slight transient skin irritation at 2.5–5 g/kg body weight, while similar treatment of rabbits at up to 0.5 g/kg body weight was without effect (Kennedy, 1986; WHO, 1991). Repeated (15- or 28-day) applications of 1–2 g/kg body weight did not induce marked local effects on the skin of rats or rabbits. The instillation of neat or 50% aqueous DMF into the rabbit eye produced moderate corneal injury and moderate to severe conjunctivitis, with some damage still evident 14 days later (Kennedy, 1986; WHO, 1991; IARC, 1999).

In a murine local lymph node assay predictive for identification of contact allergens, cell proliferation

(based on [³H]thymidine incorporation in lymph nodes) was significantly increased (324 vs. 193 decompositions per minute per lymph node in exposed and control groups, respectively) in mice (strain not specified) receiving a daily topical application of 25 µl on the dorsum of both ears for 3 consecutive days (Montelius et al., 1996). In subsequent assays, thymidine incorporation in DMF-exposed mice was up to 3-fold higher than in naive mice. However, statistical analyses were not presented, and the increase was not considered to be significant (Montelius et al., 1998). The naive (non-treated) mice were included in the protocol to measure the magnitude of vehicle (DMF)-induced proliferation. In contrast, Kimber & Weisenberger (1989) detected no difference in proliferation in a lymph node assay in which lymph node cells from DMF (the solvent)-exposed mice were compared with those from naive mice.

8.3 Short-term exposure

While there have been a number of primarily early short-term studies, these have generally been restricted to examination of specific effects following exposure to single dose levels. They are not additionally informative concerning the toxicity of DMF but confirm a range of effects in the liver, which, when considered collectively across studies, are consistent with a profile in rats of alterations in hepatic enzymes and increases in liver weight at lowest concentrations and degenerative histopathological changes, cell death, and increases in serum hepatic enzymes at higher concentrations. Although results of a short-term study in monkeys also indicate that this species is less sensitive to the effects of DMF than rats, the protocol had only one exposure concentration, and there were only two monkeys in the experiment (Hurt et al., 1991).

In the only short-term investigation in which a dose–response relationship for hepatic effects was characterized, there was a dose-related increase in liver to body weight ratio, significant at all levels of exposure, and in activity of uridine diphosphate glucuronosyl-transferase in male Wistar rats exposed for 2 weeks via drinking-water to approximately 0, 14, 70, or 140 mg/kg body weight per day (Elovaara et al., 1983). Such changes have not been observed at such low doses in more recent, longer-term studies.

Available data from acute and short-term studies also indicate that there are effects on metabolizing enzymes at very high doses (i.e., 475 mg/kg body weight per day and above administered subcutaneously to rats). These include glutathione metabolism (although reported changes at two different doses were not

N,N-Dimethylformamide

consistent) and decreases in hepatic microsomal P-450 content (Imazu et al., 1992, 1994; Fujishiro et al., 1996).

8.4 Medium-term exposure

Information on the incidences of lesions in the critical medium-term exposure studies is presented in Tables 2 and 3.

8.4.1 Inhalation

The NTP (1992a) carried out a subchronic bioassay in F344 rats, exposing males and females to 0, 50, 100, 200, 400, or 800 ppm (0, 150, 300, 600, 1200, or 2400 mg/m³) for 6 h/day, 5 days/week, for 13 weeks. The authors designated 200 ppm (600 mg/m³) as a no-observed-adverse-effect level (NOAEL) for both sexes, based upon the absence of histopathological lesions in liver. Minimal to moderate hepatocellular necrosis in both sexes was observed at 400 and 800 ppm (1200 and 2400 mg/m³), with the lesion more severe in females. However, in males, both the absolute and relative weights of liver were significantly increased at 100 ppm (300 mg/m³) and greater, although there was no clear dose-response, as weights declined at the highest dose. Serum cholesterol was increased at all levels of exposure; again, there was no clear dose-response. In males at day 24, there was a dose-related increase in serum alanine aminotransferase (ALT) (significant at all levels of exposure); however, at day 91, the increase was significant only at 400 ppm (1200 mg/m³). At day 91, there was also a dose-related increase in serum sorbitol dehydrogenase in males (significant at 200 ppm [600 mg/m³]). In females, relative liver weight was significantly increased at all levels of exposure, with the weight declining at the highest dose. Serum cholesterol was significantly increased at all levels of exposure in females, with no clear dose-response. At day 91 in females, serum sorbitol dehydrogenase and isocitrate dehydrogenase were significantly increased at 200 ppm (600 mg/m³) and greater.

Craig et al. (1984) exposed male and female F344 rats to 0, 150, 300, 600, or 1200 ppm (0, 450, 900, 1800, or 3600 mg/m³) for 6 h/day, 5 days/week, for 12 weeks. There were few overt signs of toxicity. Body weight was significantly decreased in both sexes at the highest dose. There were some changes in clinical chemistry and haematological parameters at the highest doses. In males, serum cholesterol was significantly increased at the highest concentration only. Serum alkaline phosphatase (AP) was reduced in a dose-related manner, beginning at 300 ppm (900 mg/m³). In females, cholesterol was significantly increased at 600 and 1200 ppm (1800 and 3600 mg/m³). In contrast to males, serum AP

was increased in a dose-related manner (significant at the two highest concentrations). Data on organ weights were not presented. Histopathological changes were observed in the liver at the highest doses, were “barely discernible” at 300 ppm (900 mg/m³), and were not observed at 150 ppm (450 mg/m³). The lowest-observed-adverse-effect concentration (LOAEC) for both sexes is 300 ppm (900 mg/m³), based upon slight histopathological changes in the liver (no-observed-effect concentration [NOEC] = 150 ppm [450 mg/m³]).

B6C3F1 mice were exposed to 0, 50, 100, 200, 400, or 800 ppm (0, 150, 300, 600, 1200, or 2400 mg/m³) for 6 h/day, 5 days/week, for 13 weeks (NTP, 1992a). Relative liver weight was significantly increased in both sexes at all levels of exposure, although the dose-response was not clear. Absolute liver weight was significantly increased in females at all dose levels, although the dose-response was not clear. Centrilobular hepatocellular hypertrophy (minimal to mild) was observed in all exposed males and in females at 100 ppm (300 mg/m³) and higher (lowest-observed-effect concentration [LOEC] = 50 ppm [150 mg/m³]).

Craig et al. (1984) exposed B6C3F1 mice to 0, 150, 300, 600, or 1200 ppm (0, 450, 900, 1800, or 3600 mg/m³) for 6 h/day, 5 days/week, for 12 weeks. Mortality was 10% at 600 ppm (1800 mg/m³) and 40% at 1200 ppm (3600 mg/m³). No adverse effects on haematology or clinical chemistry were observed. Hepatic cytomegaly was observed in all exposed mice; the incidence and severity were related to dose (LOEC = 150 ppm [450 mg/m³]).

Hurt et al. (1992) exposed three male and three female cynomolgus monkeys to 0, 30, 100, or 500 ppm (0, 90, 300, or 1500 mg/m³) for 6 h/day, 5 days/week, for 13 weeks. Two males were maintained for a further 13-week observation period after exposure had ceased. The protocol included microscopic examination of a comprehensive range of organ tissues in all animals. Sperm morphology and vaginal cytology were also evaluated in all animals. There were no overt signs of toxicity and no effects on body weight gain, haematology, clinical chemistry, urinalysis, organ weights, or histopathological effects attributable to DMF in cynomolgus monkeys exposed to up to 500 ppm (1500 mg/m³), leading the authors to conclude that the monkey is much less sensitive than the rat or mouse (Hurt et al., 1992).

The other inhalation studies are either poorly reported or limited in their scope (Massmann, 1956; Clayton et al., 1963; Cai & Huang, 1979; Arena et al., 1982). One group of investigators reported effects on the

Table 2: Effect levels and benchmark concentrations for DMF, inhalation exposure.

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration		
		Concentration	Response	Parameter estimates ^{a,b}	Goodness of fit	
Medium-term exposure						
B6C3F1 mice 10 males and 10 females per group 0, 50, 100, 200, 400, 800 ppm, 6 h/day, 5 days/week, for 13 weeks (NTP, 1992a)	LOEC = 50 ppm, based upon increased relative liver weight in both sexes and hepatocellular hypertrophy in males	Male, incidence (severity) of centrilobular hepatocellular hypertrophy:		BMC ₀₅ = 8.5 ppm excluding 400 and 800 ppm groups Adjusted BMC ₀₅ = 1.51 ppm	95% LCL ₀₅ = 2.5 ppm excluding 400 and 800 ppm groups Adjusted 95% LCL ₀₅ = 0.44 ppm	Chi-square (1) = 0.004 <i>P</i> -value = 0.99
		control	0/10			
		50 ppm	4/10 (1.8)			
		100 ppm	9/10 (1.3)			
		200 ppm	10/10 (2.0)			
		400 ppm	10/10 (2.0)			
		800 ppm	10/10 (2.0)			
		Female, incidence (severity) of centrilobular hepatocellular hypertrophy:		BMC ₀₅ = 17.9 ppm excluding 200, 400, and 800 ppm groups Adjusted BMC ₀₅ = 3.19 ppm excluding 200, 400, and 800 ppm groups	95% LCL ₀₅ = 8.1 ppm excluding 200, 400, and 800 ppm groups Adjusted 95% LCL ₀₅ = 1.45 ppm excluding 200, 400, and 800 ppm groups	Chi-square (1) = 7.5 <i>P</i> -value = 0.01
		control	0/10			
		50 ppm	0/10			
		100 ppm	10/10 (1.3)			
		200 ppm	10/10 (1.9)			
		400 ppm	10/10 (2.0)			
		800 ppm	10/10 (2.0)			
Long-term exposure/carcinogenicity assays						
Rat, Crl:CD BR 87 males and 87 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 2 years (Malley et al., 1994)	LOEC = 100 ppm, based upon a signif- icant increase in centrilobular hepatocellular hypertrophy (both sexes), hepatic accumulation of lipo- fuscin/haemosiderin (both sexes), and hepatic single-cell necrosis (females only) NOEC = 25 ppm	females, hepatic accumulation of lipofuscin/haemosiderin:		BMC ₀₅ = 37.0 ppm Adjusted BMC ₀₅ = 6.61 ppm	95% LCL ₀₅ = 19.8 ppm Adjusted 95% LCL ₀₅ = 3.54 ppm	Chi-square (1) = 1.01 <i>P</i> -value = 0.31
		control (<i>n</i> = 60)	8%			
		25 ppm (<i>n</i> = 59)	7%			
		100 ppm (<i>n</i> = 59)	22% (<i>P</i> < 0.05)			
		400 ppm (<i>n</i> = 62)	61% (<i>P</i> < 0.05)	BMC ₀₅ = 41.4 ppm Adjusted BMC ₀₅ = 7.39 ppm	95% LCL ₀₅ = 21.9 ppm Adjusted 95% LCL ₀₅ = 3.91 ppm	Chi-square (1) = 0.84 <i>P</i> -value = 0.36
		males, hepatic accumulation of lipofuscin/haemosiderin:				
		control (<i>n</i> = 57)	4%			
		25 ppm (<i>n</i> = 59)	4%			
		100 ppm (<i>n</i> = 58)	17% (<i>P</i> < 0.05)			
		400 ppm (<i>n</i> = 60)	58% (<i>P</i> < 0.05)	BMC ₀₅ = 44.5 ppm Adjusted BMC ₀₅ = 7.95 ppm	95% LCL ₀₅ = 23.7 ppm Adjusted 95% LCL ₀₅ = 4.23 ppm	F(1,79) = 2.09 <i>P</i> -value = 0.15
		males, relative liver weight:				
		control (<i>n</i> = 17)	2.87			
		25 ppm (<i>n</i> = 19)	2.81			
		100 ppm (<i>n</i> = 21)	3.28			
		400 ppm (<i>n</i> = 26)	3.58 (<i>P</i> < 0.05)	BMC ₀₅ = 57.7 ppm Adjusted BMC ₀₅ = 10.3 ppm	95% LCL ₀₅ = 37.8 ppm Adjusted 95% LCL ₀₅ = 6.75 ppm	Chi-square (2) = 1.71 <i>P</i> -value = 0.42
		males, hepatic foci of alterations (clear cell):				
		control (<i>n</i> = 57)	11%			
		25 ppm (<i>n</i> = 59)	8%			
		100 ppm (<i>n</i> = 58)	22% (<i>P</i> < 0.05)			
		400 ppm (<i>n</i> = 60)	35% (<i>P</i> < 0.05)			

Table 2 (contd).

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration	
		Concentration	Response	Parameter estimates ^{a,b}	Goodness of fit
Rat, Crl:CD BR 87 males and 87 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 2 years (Malley et al., 1994)	LOEC = 100 ppm, based upon a signifi- cant increase in centri- lobular hepatocellular hypertrophy (both sexes), hepatic accumulation of lipofuscin/haemosideri n (both sexes), and hepatic single-cell necrosis (females only) NOEC = 25 ppm	females, hepatic foci of alterations (clear cell): control (n = 60) 5% 25 ppm (n = 59) 5% 100 ppm (n = 59) 14% 400 ppm (n = 62) 24% (P < 0.05)		BMC ₀₅ = 84.3 ppm Adjusted BMC ₀₅ = 15.1 ppm	95% LCL ₀₅ = 53.4 ppm Adjusted 95% LCL ₀₅ = 9.54 ppm Chi-square (2) = 0.77 P-value = 0.68
		females, relative liver weight: control (n = 22) 3.12 25 ppm (n = 14) 3.43 100 ppm (n = 12) 3.33 400 ppm (n = 23) 3.86 (P < 0.05)		BMC ₀₅ = 101.6 ppm Adjusted BMC ₀₅ = 18.1 ppm	95% LCL ₀₅ = 46.2 ppm Adjusted 95% LCL ₀₅ = 8.25 ppm F(1,67) = 1.12 P-value = 0.29
		males, centrilobular hepatocellular hypertrophy: control (n = 57) 0 25 ppm (n = 59) 0 100 ppm (n = 58) 5% (P < 0.05) 400 ppm (n = 60) 30% (P < 0.05)		BMC ₀₅ = 118.7 ppm Adjusted BMC ₀₅ = 21.2 ppm	95% LCL ₀₅ = 56.4 ppm Adjusted 95% LCL ₀₅ = 10.1 ppm Chi-square (1) = 0.65 P-value = 0.42
		females, centrilobular hepatocellular hypertrophy: control (n = 60) 0 25 ppm (n = 59) 0 100 ppm (n = 59) 3% (P < 0.05) 400 ppm (n = 62) 40% (P < 0.05)		BMC ₀₅ = 126.7 ppm Adjusted BMC ₀₅ = 22.6 ppm	95% LCL ₀₅ = 77.7 ppm Adjusted 95% LCL ₀₅ = 13.9 ppm Chi-square (1) = 0.13 P-value = 0.72
		females, hepatic single-cell necrosis: control (n = 60) 0 25 ppm (n = 59) 0 100 ppm (n = 59) 5% (P < 0.05) 400 ppm (n = 62) 18% (P < 0.05)		BMC ₀₅ = 126.9 ppm Adjusted BMC ₀₅ = 22.7 ppm	95% LCL ₀₅ = 72.9 ppm Adjusted 95% LCL ₀₅ = 13.0 ppm Chi-square (1) = 0.78 P-value = 0.38
Mice, Crl:CD 1 (ICR)BR 78 males and 78 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 18 months (Malley et al., 1994)	LOEC = 25 ppm, based upon centrilobular hepatocellular hyper- trophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males)	females, hepatic single-cell necrosis: control (n = 61) 29% 25 ppm (n = 63) 44% (P < 0.05) 100 ppm (n = 61) 70% (P < 0.05) 400 ppm (n = 63) 76% (P < 0.05)		BMC ₀₅ = 16.8 ppm BMC ₀₅ = 5.9 ppm excluding 400 ppm group Adjusted BMC ₀₅ = 3.00 ppm BMC ₀₅ = 1.05 ppm excluding 400 ppm group	95% LCL ₀₅ = 11.9 ppm 95% LCL ₀₅ = 4.1 ppm excluding 400 ppm group Adjusted 95% LCL ₀₅ = 2.13 ppm 95% LCL ₀₅ = 0.73 ppm excluding 400 ppm group Chi-square (2) = 9.7 P-value = 0.00 (Chi-square (1) = 0.02 P-value = 0.88)
		males, hepatic single-cell necrosis: control (n = 60) 24% 25 ppm (n = 62) 59% (P < 0.05) 100 ppm (n = 60) 68% (P < 0.05) 400 ppm (n = 59) 87% (P < 0.05)		BMC ₀₅ = 10.8 ppm Adjusted BMC ₀₅ = 1.93 ppm	95% LCL ₀₅ = 7.8 ppm Adjusted 95% LCL ₀₅ = 1.39 ppm Chi-square (2) = 13.4 P-value = 0.00
		males, hepatic Kupffer cell hyperplasia/pigment accumulation: control (n = 60) 22% 25 ppm (n = 62) 52% (P < 0.05) 100 ppm (n = 60) 60% (P < 0.05) 400 ppm (n = 59) 86% (P < 0.05)		BMC ₀₅ = 11.1 ppm Adjusted BMC ₀₅ = 1.98 ppm	95% LCL ₀₅ = 8.2 ppm Adjusted 95% LCL ₀₅ = 1.46 ppm Chi-square (2) = 7.5 P-value = 0.02

Table 2 (contd).

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration	
		Concentration	Response	Parameter estimates ^{a,b}	Goodness of fit
Mice, Crl:CD 1 (ICR)BR 78 males and 78 females per group 0, 25, 100, 400 ppm, 6 h/day, 5 days/week, for 18 months (Malley et al., 1994)	LOEC = 25 ppm, based upon centrilobular hepatocellular hyper- trophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males)	females, hepatic Kupffer cell hyperplasia/pigment accumulation: control (<i>n</i> = 61) 51% 25 ppm (<i>n</i> = 63) 57% 100 ppm (<i>n</i> = 61) 71% (<i>P</i> < 0.05) 400 ppm (<i>n</i> = 63) 89% (<i>P</i> < 0.05)		BMC ₀₅ = 13.4 ppm Adjusted BMC ₀₅ = 2.39 ppm	95% LCL ₀₅ = 9.3 ppm Adjusted 95% LCL ₀₅ = 1.66 ppm Chi-square (2) = 0.35 <i>P</i> -value = 0.84
		males, centrilobular hepatocellular hypertrophy: control (<i>n</i> = 60) 0 25 ppm (<i>n</i> = 62) 8% (<i>P</i> < 0.05) 100 ppm (<i>n</i> = 60) 41% (<i>P</i> < 0.05) 400 ppm (<i>n</i> = 59) 52% (<i>P</i> < 0.05)		BMC ₀₅ = 18.9 ppm Adjusted BMC ₀₅ = 3.38 ppm BMC ₀₅ = 2.93 ppm excluding 400 ppm group	95% LCL ₀₅ = 15.3 ppm Adjusted 95% LCL ₀₅ = 0.95 ppm 95% LCL ₀₅ = 1.48 ppm excluding 400 ppm group Chi-square (2) = 0.77 <i>P</i> -value = 0.00 (Chi-square (0) = 0.00 <i>P</i> -value = 1.00)
		females, centrilobular hepatocellular hypertrophy: control (<i>n</i> = 61) 0 25 ppm (<i>n</i> = 63) 6% 100 ppm (<i>n</i> = 61) 19% (<i>P</i> < 0.05) 400 ppm (<i>n</i> = 63) 54% (<i>P</i> < 0.05)		BMC ₀₅ = 25.1 ppm Adjusted BMC ₀₅ = 4.48 ppm	95% LCL ₀₅ = 19.9 ppm Adjusted 95% LCL ₀₅ = 3.55 ppm Chi-square (2) = 0.39 <i>P</i> -value = 0.82
		males, relative liver weight: control (<i>n</i> = 31) 5.85 25 ppm (<i>n</i> = 42) 5.94 100 ppm (<i>n</i> = 38) 7.06 (<i>P</i> < 0.05) 400 ppm (<i>n</i> = 36) 7.80 (<i>P</i> < 0.05)		BMC ₀₅ = 65.6 ppm Adjusted BMC ₀₅ = 11.7 ppm	95% LCL ₀₅ = 37.5 ppm Adjusted 95% LCL ₀₅ = 6.69 ppm F(1,143) = 1.94 <i>P</i> -value = 0.17
		females, relative liver weight: control (<i>n</i> = 42) 5.59 25 ppm (<i>n</i> = 35) 5.71 100 ppm (<i>n</i> = 36) 5.99 400 ppm (<i>n</i> = 47) 6.35 (<i>P</i> < 0.05)		BMC ₀₅ = 144.7 ppm Adjusted BMC ₀₅ = 25.8 ppm	95% LCL ₀₅ = 76.3 ppm Adjusted 95% LCL ₀₅ = 13.6 ppm F(1,156) = 0.34 <i>P</i> -value = 0.56

^a Adjusted from intermittent exposure (h/day, days/week) to continuous exposure.

^b LCL = Lower confidence limit.

Table 3: Effect levels and benchmark doses for DMF, oral exposure.

Study (reference)	Effect level	Data for calculating benchmark dose		Benchmark dose		
		Dose (mg/kg body weight per day)	Response	Parameter estimates	Goodness of fit	
Medium-term exposure						
Rat, Wistar 25 males and 25 females per group Dietary administration for 15 weeks (Becci et al., 1983)	LOEL = 69 mg/kg body weight per day, based upon a significant increase in relative liver weight in females at the two highest doses (NOEL = 20 mg/kg body weight per day)	males, relative liver weight:		BMD ₀₅ = 23.1 mg/kg body weight per day	95% LCL ₀₅ = 12.7 mg/kg body weight per day	F(1,92) = 0.73 <i>P</i> -value = 0.39
		control (<i>n</i> = 25)				
		18 (<i>n</i> = 23)				
		61 (<i>n</i> = 25)				
		210 (<i>n</i> = 23)				
		4.99 ± 0.10 (<i>P</i> < 0.05)				
		females, relative liver weight:		BMD ₀₅ = 35.9 mg/kg body weight per day	95% LCL ₀₅ = 15.7 mg/kg body weight per day	F(1,94) = 0.13 <i>P</i> -value = 0.72
		control (<i>n</i> = 25)				
		20 (<i>n</i> = 25)				
		69 (<i>n</i> = 24)				
		235 (<i>n</i> = 24)				
		00 ± 0.12 (<i>P</i> < 0.05)				
Mouse, CD-1 30 males and 30 females per group dietary administration for 17 weeks (Becci et al., 1983)	LOEL = 96 mg/kg body weight per day, based upon statistically significant increase in relative liver weight in females (NOEL = 28 mg/kg body weight per day)	males, relative liver weight:		BMD ₀₅ = 21.3 mg/kg body weight per day	95% LCL ₀₅ = 7.6 mg/kg body weight per day	F(1,112) = 1.17 <i>P</i> -value = 0.28
		control (<i>n</i> = 30)				
		22 (<i>n</i> = 28)				
		70 (<i>n</i> = 29)				
		246 (<i>n</i> = 29)				
		6.6 ± 0.1 (<i>P</i> < 0.01)				
		females, relative liver weight:		BMD ₀₅ = 36.8 mg/kg body weight per day	95% LCL ₀₅ = 21.3 mg/kg body weight per day	F(1,114) = 0.14 <i>P</i> -value = 0.71
		control (<i>n</i> = 30)				
		28 (<i>n</i> = 29)				
		96 (<i>n</i> = 29)				
		326 (<i>n</i> = 30)				
		6.6 ± 0.3 (<i>P</i> < 0.01)				

Concise International Chemical Assessment Document 31

liver of rats exposed to DMF vapour for 18 weeks at a concentration of just 7.3 ppm (21.9 mg/m³) (no further details provided in the citation) (Cai & Huang, 1979). Myocardial changes occurred in rabbits exposed to 40 ppm (120 mg/m³) for 50 days (Arena et al., 1982).

8.4.2 Oral

In a 90-day dietary study, Crl:CD rats were exposed to 0, 10, 50, or 250 mg/kg body weight per day (Haskell Laboratory, 1960; Kennedy & Sherman, 1986). Mild effects on the liver (enlargement of hepatic cells) and haematological effects (anaemia, leukocytosis) were observed at 50 mg/kg body weight per day; at the top dose of 250 mg/kg body weight per day, weight gain was reduced, and the animals had slight anaemia, leukocytosis, and liver cell enlargement. Although there was an apparent increase in serum cholesterol in both sexes at the highest dose, statistical analyses were not presented. The no-observed-effect level (NOEL) was 10 mg/kg body weight per day. The lowest-observed-effect level (LOEL) is 50 mg/kg body weight per day, based upon a significant increase in relative liver weight in males.

In a second study involving larger group sizes, a different strain (Wistar), and more comprehensive tissue examination, growth was inhibited but no tissue lesions were observed in rats administered DMF in the diet for 15 weeks (Becci et al., 1983). Males received 0, 18, 61, or 210 mg/kg body weight per day, and females received 0, 20, 69, or 235 mg/kg body weight per day. The LOEL is 69 mg/kg body weight per day, based upon a significant increase in relative liver weight in females at the two highest doses (NOEL = 20 mg/kg body weight per day).

In the corresponding study in CD-1 mice involving dietary administration (males: 0, 22, 70, or 246 mg/kg body weight per day; females: 0, 28, 96, or 326 mg/kg body weight per day) for 17 weeks, there were no overt signs of toxicity and no notable effects on blood morphology, blood biochemistry, or urinary parameters (Becci et al., 1983). Microscopic examination of an extensive range of organ tissues revealed only mild effects on the liver in the majority of high-dose males and females. There was a dose-related increase in relative liver weight at all dose levels, although this was statistically significant only in the mid- and high-dose females and in the high-dose males. On this basis, the LOEL is 96 mg/kg body weight per day, based upon a significant increase in relative liver weight in females (NOEL = 28 mg/kg body weight per day).

In a submission to the US EPA Office of Toxic Substances, BASF (1984) reported that there were no adverse effects observed in beagle dogs (four males and four females per group) administered 0, 1.4, 7.0, or 34.8 mg/kg body weight per day (NOEL) in the diet for 13 weeks. The protocol included measurement of food consumption, measurement of body weight gain, hearing tests, ophthalmoscopic examination, clinical laboratory investigations, measurement of organ weights, and histopathological observations.

8.5 Long-term exposure and carcinogenicity

Information on the incidences of lesions in critical long-term studies is presented in Tables 2 and 3.

8.5.1 Inhalation

Malley et al. (1994) exposed Crl:CD BR rats for 6 h/day, 5 days/week, to 0, 25, 100, or 400 ppm (0, 75, 300, or 1200 mg/m³) DMF vapour for 24 months. There were no overt signs of toxicity other than a reduction in weight gain in the rats exposed at 400 ppm (1200 mg/m³) and, to a lesser extent and towards the end of the study, in males exposed at 100 ppm (300 mg/m³). Haematological findings were normal, as were urinary analyses. There was a concentration-related increase in serum sorbitol dehydrogenase activity (indicative of hepatic effects) in the male and female rats at 100 and 400 ppm (300 and 1200 mg/m³). Relative liver weights were increased in both sexes at 400 ppm (1200 mg/m³), and microscopic examination revealed hepatic lesions (centrilobular hepatocellular hypertrophy, lipofuscin/haemosiderin accumulation, clear cell foci, and single-cell necrosis in males and high-dose females and focal cystic degeneration in males) at 100 and 400 ppm (300 and 1200 mg/m³). Microscopic examination of an extensive range of tissues from the high-dose animals (and of selected tissues from the lower dose groups) revealed no other treatment-related lesions except in females, in which there was an increased incidence of uterine endometrial stromal polyps (1.7%, 5.1%, 3.4%, and 14.8% for control, low-, mid-, and high-dose females, respectively). Historical control data from the same laboratory indicated a highly variable incidence of endometrial stromal polyps (2–15% for 14 control groups, average 6.6%). The investigators concluded that DMF was not carcinogenic to rats under the conditions of exposure. The LOEC was 100 ppm (300 mg/m³) (NOEC = 25 ppm [75 mg/m³]), based upon a significant increase in centrilobular hepatocellular hypertrophy (both sexes), significant increase in hepatic accumulation of lipofuscin/haemosiderin (both sexes), and hepatic single-cell necrosis (females only).

Mice [CrI:CD 1 (ICR)BR] were exposed to 0, 25, 100, or 400 ppm (0, 75, 300, or 1200 mg/m³) DMF for 6 h/day, 5 days/week, for 18 months (Malley et al., 1994). Haematological observations were normal. Relative liver weight was significantly increased at the two highest concentrations in males. Microscopic alterations in liver were observed at all levels of exposure. The authors concluded that DMF was not carcinogenic to mice under the conditions of the bioassay. The LOEC is 25 ppm (75 mg/m³), based upon centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males).

8.5.2 Oral

An inadequate carcinogenicity study involving the administration of DMF in the drinking-water of BD rats at approximately 10 or 20 mg/kg body weight per day for 500 or 250 days, respectively, provided no evidence of tumour formation, although the extent of tissue examination was not specified (Druckrey et al., 1967). In female Mongolian gerbils administered DMF in the drinking-water at concentrations of 1.0–6.6% (around 5–40 mg/kg body weight per day) for up to 200 days, there were many early deaths at concentrations of 1.7% (around 7–11 mg/kg body weight per day) and above, and all DMF-exposed groups had liver degeneration and kidney congestion (Llewellyn et al., 1974).

8.5.3 Injection

In a study in hamsters investigating the carcinogenic activity of aflatoxins, there was no mention of any tumours in the DMF-treated controls. These animals (five males and five females) received weekly intraperitoneal injections of 0.1 ml of a 50% DMF solution (equivalent to approximately 47 mg DMF/kg body weight per injection) for 6–8.5 months and were then maintained untreated until they died (average life span 19 months) (Herrold, 1969). Although there were no increases in tumours following repeated intraperitoneal injections of DMF to rats for 10 weeks in a study reported in a secondary source, available information was inadequate to permit critical review (Kommineni, 1973).

8.6 Genotoxicity and related end-points

The following discussion is limited to results of assays for gene mutation and cytogenesis, i.e., those assays in which the end-points are most relevant to the assessment of DMF with respect to human health.

The results of assays for gene mutation *in vitro* were almost entirely negative. Of 20 identified assays in

Salmonella, results were negative in 18 (Green & Savage, 1978; Purchase et al., 1978; Baker & Bonin, 1981; Brooks & Dean, 1981; Garner et al., 1981; Gatehouse, 1981; Ichinotsubo et al., 1981; MacDonald, 1981; Martire et al., 1981; Nagao & Takahashi, 1981; Richold & Jones, 1981; Rowland & Severn, 1981; Simmon & Shepherd, 1981; Skopek et al., 1981; Venitt & Crofton-Sleigh, 1981; Antoine et al., 1983; Falck et al., 1985; Mortelmans et al., 1986), and two had equivocal results (Hubbard et al., 1981; Trueman, 1981). Results in six assays in *Escherichia coli* were all negative (Gatehouse, 1981; Matsushima et al., 1981; Mohn et al., 1981; Thomson, 1981; Venitt & Crofton-Sleigh, 1981; Falck et al., 1985).

Although fewer assays for cytogenetic effects and genotoxicity *in vitro* were identified than for gene mutation, results were also predominantly negative. In assays for chromosomal aberrations (CAs), results were negative for human lymphocytes (Antoine et al., 1983) and Chinese hamster ovary (CHO) (Natarajan & van Kesteren-van Leeuwen, 1981) and weakly positive in human peripheral lymphocytes (Koudela & Spazier, 1979). In three mouse lymphoma assays, results were negative (Jotz & Mitchell, 1981; Mitchell et al., 1988; Myhr & Caspary, 1988) and one was weakly positive (McGregor et al., 1988). Results of *in vitro* tests for sister chromatid exchange (SCE) were negative in three assays in CHO (Evans & Mitchell, 1981; Natarajan & van Kesteren-van Leeuwen, 1981; Perry & Thomson, 1981) and one in human lymphocytes (Antoine et al., 1983). Assays for unscheduled DNA synthesis (UDS) were negative in human fibroblasts (Agrelo & Amos, 1981; Robinson & Mitchell, 1981), mouse hepatocytes (Klaunig et al., 1984), and HeLa cells (Martin & McDermid, 1981), while in assays in rat hepatocytes, results were both negative (Ito, 1982) and positive (Williams, 1977). Results of assays for DNA repair in mouse (McQueen et al., 1983) and hamster (McQueen et al., 1983) hepatocytes were also negative. An assay for DNA repair in human hepatocytes had negative results (McQueen et al., 1988).

The database for genotoxicity studies *in vivo* is more limited than that for *in vitro* studies.

In two adequate assays for micronucleus induction, results were negative (Kirkhart, 1981; Antoine et al., 1983). In the latter study, dose levels were too widely spaced, and the top dose was 2000 mg/kg body weight. Results were also negative in two assays in which there were no positive controls (Salamone et al., 1981; Tsuchimoto & Matter, 1981). It should be noted that Salamone et al. (1981) observed no effect at doses up to 80% of the LD₅₀. An assay in which an increase in

Concise International Chemical Assessment Document 31

micronuclei was observed in bone marrow of mice was reported only as an abstract (Ye, 1987), although a dose-response was not clear. Although six dose levels were included in the protocol, the highest dose was only 20 mg/kg body weight (oral LD₅₀ values in laboratory animals range from 2000 to 7000 mg/kg body weight).

Negative results were reported in assays for chromosomal damage in bone marrow of rats (Sheveleva et al., 1979; McGregor, 1981) and dominant lethal assays in rats (Lewis et al., 1979; McGregor, 1981; Cragin et al., 1990). Limited reporting (abstracts, secondary sources) precluded critical review of these studies.

Quantitative data were not presented in a report of an assay in which SCEs were not observed in bone marrow of mice (Paika et al., 1981).

8.7 Reproductive toxicity

8.7.1 Effects on fertility

Effects on organ weights or histopathological effects in the reproductive organs have not been observed in medium-term or long-term studies in rats or mice following inhalation or oral exposure (Becci et al., 1983; Craig et al., 1984; Kennedy & Sherman, 1986; NTP, 1992a; Malley et al., 1994). In several of these bioassays, additional reproductive end-points were examined. These included sperm density, motility, or count and length of diestrus in rats and mice exposed for 13 weeks to concentrations up to 800 ppm (2400 mg/m³) (NTP, 1992a) and semen volume and sperm motility, morphology, or count in a limited number of monkeys exposed to 500 ppm (1500 mg/m³) (Hurt et al., 1992). In none of these investigations, however, were there adverse effects on reproductive parameters at concentrations or doses less than those at which hepatic effects were observed; indeed, the only effect reported was prolonged diestrus in female rats exposed to 800 ppm (2400 mg/m³) for 13 weeks (NTP, 1992a).

Few studies were identified in which the protocols were designed specifically to address reproductive toxicity. In a study reported as abstracts (Lewis et al., 1979; Cragin et al., 1990), exposure of male Sprague-Dawley rats to 30 or 300 ppm (90 or 900 mg/m³) for 6 h/day for 5 days did not result in histopathological changes in reproductive organs after 6 weeks. Pairing of the exposed males with unexposed females for 6 weeks after exposure resulted in a reduced number of viable fetuses per dam in the low-dose group only.

In a multi-generation study in Swiss mice, DMF was administered in the drinking-water at concentrations

of 0, 1000, 4000, or 7000 mg/litre (NTP, 1992b; Fail et al., 1998). Litters from F0 animals were sacrificed immediately. At week 16, pairs were separated and the final litters reared to postnatal day 21, then entered into an F1 fertility assessment. A crossover mating trial was also carried out with the F0 mice. The lowest level of exposure (1000 mg/litre; average 219 mg/kg body weight per day) was designated by the authors as the maximum tolerated dose (LOEL) for the F0 mice, based upon increased relative liver weight in males and females and increased relative kidney and adrenal weight in females. Reproductive effects in F0 mice included reduced fertility and fecundity at 4000 and 7000 mg/litre. The crossover trial identified females as the affected sex. Following F1 mating, both F2 litter size and live pup weight were reduced at all doses. At necropsy, the body weight of F1 males and females was reduced at the two highest doses, and both absolute and relative liver weights were increased at all doses. The authors concluded that both reproductive and developmental toxicity occurred at the two highest doses (4000 and 7000 mg/litre) in the F0 mice and at all dose levels (1000 mg/litre) in the F1 mice.

No abnormalities were observed in sperm in an adequate single-injection study in mice, for which few details were presented (Antoine et al., 1983). Although negative results were reported in other assays in mice, quantitative data were not presented (Topham, 1980, 1981) or only a secondary source was available (McGregor, 1981).

8.7.2 Developmental toxicity

The database on developmental toxicity is more extensive, with numerous studies having been conducted in various species by the inhalation, oral, and dermal routes. Emphasis here is on the most recent studies for which protocols and reporting are most extensive.

In studies in which DMF has been administered by inhalation or ingestion, it has been, at most, weakly teratogenic, with malformations being observed only at high doses that were maternally toxic (450 ppm [1350 mg/m³] by inhalation in rabbits; 503 mg/kg body weight per day following ingestion in rats), based on consideration of maternal body weight and signs of overt toxicity (Hellwig et al., 1991). In general, DMF has induced primarily fetotoxic effects most often at maternally toxic concentrations or doses (100 mg/kg body weight per day by stomach tube in rats) (Saillenfait et al., 1997) but occasionally in the absence of maternal toxicity, based on determination of body weight gain and overt signs. For example, Lewis et al. (1992) reported maternal weight gain in Crl:CD rats at 300 ppm (900

mg/m³) (maternal LOEC), but not at 30 ppm (90 mg/m³), at which concentration there was a slight but significant reduction in fetal weight. The mean fetal weights of control, low-dose, and high-dose groups were 5.5 ± 0.2 , 5.5 ± 0.4 , and 5.3 ± 0.2 g, respectively ($P < 0.05$ for both low- and high-dose groups).

The pattern of results of studies by the dermal route was similar, with malformations being observed in rats only at doses that were maternally toxic based on examination of weight gain and overt signs of toxicity only (944 mg/kg body weight per day in rats; 400 mg/kg body weight per day in rabbits; 944 mg/kg body weight per day in mice) (Hellwig et al., 1991). In one of the relatively recent investigations by other authors (Hansen & Meyer, 1990), fetotoxic effects (delayed ossification) only were observed at doses (945 mg/kg body weight per day) at which there were no effects on maternal weight gain and no overt signs of maternal toxicity.

Klug et al. (1998) carried out a mouse limb bud assay with DMF, HMMF, NMF, SMG (a synthesis product of glutathione and methyl isocyanate), *S*-(*N*-methyl-carbamoyl)cysteine (SMC), *N*-acetoximethyl-*N*-methylformamide (AMMF), AMCC, L-cysteine, and glutathione. There were no signs of adverse developmental effects caused by DMF, NMF, HMMF, AMMF, L-cysteine, or glutathione. However, a pronounced impact upon growth and development was observed for AMCC, SMC, and SMG (metabolites resulting from the glutathione binding pathway). The authors concluded that the developmental toxicity of DMF in different species is related to the magnitude of glutathione binding.

8.8 Neurological effects

In male Wistar rats exposed to 0, 7, 35, or 65 mg DMF/kg body weight per day in drinking-water for either 2 or 7 weeks, glial cell fractions were isolated from the left cerebral hemisphere and assayed for activity of acid proteinase and 2',3'-cyclic nucleotide 3'-phosphohydrolase (Savolainen, 1981). The right cerebral hemisphere was assayed for RNA, glutathione, and activities of succinate dehydrogenase and azoreductase. After 2 weeks, there was a dose-related increase in activity of 2',3'-cyclic nucleotide 3'-phosphohydrolase, which was significant ($P < 0.001$) at all levels of exposure. After 7 weeks of exposure to 0, 8, 39, or 75 mg/kg body weight per day, the intake of drinking-water was significantly reduced at all levels of exposure. There was also a significant reduction in activity of azoreductase and succinate dehydrogenase (uneven dose-response).

9. EFFECTS ON HUMANS

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations consistently indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with related symptoms, increases in serum hepatic enzymes, and histopathological effects being reported.

9.1 Effects on the liver

Case reports in workers acutely exposed to DMF confirm that the liver is the target organ, with hepatic effects and associated disorders of the digestive system being reported. Symptoms include abdominal pain, anorexia, incoordination, and jaundice, as well as nausea, vomiting, and diarrhoea; nasal and skin irritation have also been reported (Tolot et al., 1968; Potter, 1973; Chary, 1974; Chivers, 1978; Guirguis, 1981; Paoletti et al., 1982a, 1982b; Riachi et al., 1993; Drouet D'Aubigny et al., 1998; Huang et al., 1998). Changes in both liver function (Weiss, 1971; Potter, 1973; Guirguis, 1981; Paoletti et al., 1982b; Riachi et al., 1993; Drouet D'Aubigny et al., 1998) and morphology (Tolot et al., 1968; Riachi et al., 1993) have also been observed. In one of the few reports where there was some indication of magnitude of exposure, hepatic impairment (marked increases in serum levels of ALT, aspartate aminotransferase [AST], AP, and bilirubin, together with fulminant hepatitis and jaundice) was reported in a woman who ingested about 0.6 g DMF/kg body weight (in a formulation containing other ingredients) in a suicide attempt (Nicolas et al., 1990). Similarly, clinical measurements were carried out in a patient who intravenously injected (presumably) 50 ml of a veterinary euthanasia drug containing DMF as a solvent (Buylaert et al., 1996). Serum AST and ALT increased, there was a transient rise in total serum bilirubin, and prothrombin time decreased. AP levels remained within the normal range.

Alcohol intolerance, characterized by flushing of the face, dizziness, nausea, and tightness of the chest, has been widely reported among DMF-exposed workers (Lyle, 1979; Lyle et al., 1979; Lauwerys et al., 1980; Yonemoto & Suzuki, 1980; Paoletti & Iannaccone, 1982; Paoletti et al., 1982a; Tomasini et al., 1983; Cirila et al., 1984; Redlich et al., 1988, 1990; Wang et al., 1989, 1991; Cai et al., 1992; Fiorita et al., 1997; Wrbitzky, 1999). While it is difficult to establish with

Concise International Chemical Assessment Document 31**Table 4: Effects of DMF exposure on hepatic function in humans.^a**

Concentration ^b	Effect on liver enzymes	Exposed population	Confounders	Reference
<10–60 ppm; random area sampling	increase	183 workers	some workers were also exposed to solvents	Wang et al. (1989, 1991)
10–42 ppm; area monitoring	increase	13 workers	few details reported	Yang et al. (1994)
1–27 ppm	no effect	27 workers		Paoletti & Iannaconne (1982)
5–20 ppm	increase (significance not reported)	13 workers	exposure to solvents	Tomasini et al. (1983)
3–20 ppm (TWA, 7 ppm); personal sampling	significant increase	100 workers		Cirla et al. (1984)
0.3–15.5 ppm (usually <10 ppm); static area sampling	no effect	22 workers		Lauwerys et al. (1980)
1–5 ppm; personal and area sampling	no effect	6 workers		Yonemoto & Suzuki (1980)
4–8 ppm (mean 6 ppm); sampling not specified	no effect	28 workers		Catenacci et al. (1984)
0.2–8 ppm; area sampling	increase (significance not reported)	26 workers	concomitant exposure to acrylonitrile	Major et al. (1998)
7 ppm; area sampling at different workplaces	significant increase	75 workers		Fiorito et al. (1997)
0.1–7 ppm; personal sampling	no effect	207 workers	some workers were also exposed to toluene	Cai et al. (1992)
up to 2.3 ppm; personal sampling	no effect	126 workers		Wrbitzky & Angerer (1998); Wrbitzky (1999)

^a See text for more detailed descriptions of highlighted studies.^b 1 ppm = 3 mg/m³.

any certainty a lowest concentration at which increases in these subjective symptoms first appear, they have been associated with mean or median levels of 10 ppm (30 mg/m³) (Lauwerys et al., 1980; Yonemoto & Suzuki, 1980; Cai et al., 1992; Fiorito et al., 1997); in a recent study, some workers reported symptoms upon exposure to concentrations for which the median value was as low as 1.2 ppm (3.6 mg/m³) (Wrbitzky, 1999).

Levels of serum hepatic enzymes in populations occupationally exposed to DMF have been determined in several cross-sectional studies. A brief overview of the information on exposure–response derived from these studies is summarized in Table 4.

While there have been considerable variations in the size of study populations, magnitude and duration of exposure, extent of exposure to other substances, and adequacy of reporting in these investigations, there is a consistent pattern of increase in serum enzymes in workers with relatively higher exposures in these investigations, some of which included individual monitoring. In summary, the results concerning exposure–response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations

in the range of 1–6 ppm (3–18 mg/m³). At higher levels of exposure (>7 ppm [>21 mg/m³]), increased serum levels of hepatic enzymes have been observed consistently.

There were three studies identified (highlighted in Table 4) for which TWA exposures were presented and which can serve, therefore, as the basis for at least crude estimates of exposure–response. These are described in more detail here. It should be noted, though, that the monitored levels in these studies do not take into account potential additional dermal exposure.

In a carefully conducted investigation of liver function in 75 workers in a synthetic leather factory, geometric mean levels of DMF in the air based on 8-h area sampling in various working locations were approximately 20 mg/m³ (~7 ppm) (range 2–40 mg/m³) (Fiorito et al., 1997). It was reported that the study subjects worked in a factory that produces synthetic leather using polyurethane resin, pigments, and large amounts of DMF (about 14 tonnes/day), where skin contact with liquid DMF was also possible. The mean duration of employment was 3.8 years. The control group consisted of 75 unexposed workers similar in age, sex, social status, and residence. Confounding by

alcohol consumption and pre-existing liver disease was minimized through selection criteria for study subjects. Analysis of paired enzymes was also conducted. All workers underwent a complete physical examination, with liver function tests for serum AST, ALT, (γ -glutamyl transpeptidase (γ -GT), AP, bile acids (BA), bilirubin, serum cholesterol and triglycerides, and markers for hepatitis A, B, and C. Gastrointestinal symptoms (stomach pain, nausea, appetite loss) were reported by 50% of the DMF-exposed workers, and 40% had symptoms such as face flushing, palpitation, headache, dizziness, or tremors following alcohol consumption. (Many avoided alcohol as a result.) Mean serum ALT (28.8 vs. 21.9 IU/litre), AST (26.5 vs. 21.1 IU/litre), (γ -GT (29.5 vs. 14.2 IU/litre), and AP (75.7 vs. 60.8 IU/litre) were significantly higher in 12 of 75 workers in the exposed group ($P < 0.001$); 17/75 (23%) had abnormal liver function, compared with only 4% of controls. Multivariate analyses confirmed that ALT, AST, and (γ -GT were significantly correlated with cumulative DMF exposure. The analyses controlled for factors such as body mass index, alcohol intake, serum cholesterol, and hepatitis markers, which did not explain the observed effects.

Catenacci et al. (1984) investigated liver function (serum glutamate-oxalate transaminase [SGOT], serum glutamate-pyruvate transaminase [SGPT], (γ -GT, and AP) in workers employed for at least 5 years in an acrylic fibre plant; no mention was made of exposure to other solvents. The first group of 28 subjects worked in the spinning department, where DMF exposure (8-h TWA) ranged from 12 to 25 mg/m³, with a mean of 18 mg/m³ (4–8 ppm, mean 6 ppm). The second group consisted of 26 subjects exposed, in the polymer department, to DMF at (8-h TWA) 1.8–5 mg/m³, with a mean of 3 mg/m³ (0.6–1.8 ppm, mean 1 ppm). A control group consisted of 54 subjects matched for age, smoking/alcohol consumption, and history of liver disease, who had never been occupationally exposed to solvents. The data on which the estimated TWA exposures were based were not reported. Mean serum values for SGOT (20.74, 21.06, and 20.17 mU/ml for 6 ppm, 1 ppm, and control groups, respectively), SGPT (19.76, 21.26, and 26.09 mU/ml for 6 ppm, 1 ppm, and control groups, respectively), (γ -GT (36.37, 28.34, and 40.76 mU/ml for 6 ppm, 1 ppm, and control groups, respectively), and AP (154.42, 150.35, and 153.07 mU/ml for 6 ppm, 1 ppm, and control groups, respectively) did not differ among the three groups and were within the normal ranges. Few additional details were presented in the published account of this study.

Cirila et al. (1984) carried out a clinical evaluation of 100 workers in synthetic polyurethane leather produc

tion exposed to a mean TWA concentration (determined by personal sampling) of 22 mg/m³ (range 8–58 mg/m³) (mean TWA 7 ppm; range 3–19 ppm). The mean exposure period was 5 years (range 1–15 years). The workers were also exposed to small (but unspecified) quantities of toluene, methyl ethyl ketone (MEK), ethyl acetate, and isopropyl and isobutyl alcohol. Study subjects were selected to minimize large variations in exposure; those with histories of possible accidental exposures were also excluded. The referent group was 100 workers at the same or similar factories, without exposure to any solvents or toxic metals, matched by sex, age group, alcohol history, smoking habits, coffee intake, socio-economic status, residence, and dietary customs. Clinical evaluation was carried out and a laboratory assessment was performed for blood cell counts and serum AP, AST, ALT, and (γ -GT. Serum (γ -GT was abnormally high in 25/100 exposed and only 10/100 referents ($P < 0.01$). Higher prevalences in the exposed group for abnormally high serum levels of AST (9 vs. 3) and ALT (12 vs. 8) were not statistically significant. AP values were normal in all subjects. When subjects who had not modified their alcohol consumption upon working with DMF were considered, the effect was still evident. Several symptoms, including headache, dyspepsia, and digestive impairment, characteristic of effects on the liver were also associated with exposure to DMF.

Histopathological changes in liver have also been reported in occupationally exposed workers, although quantitative data on levels of exposure are not well documented. Tomasini et al. (1983) reported hepatic pain and palpable liver in 4 of 13 workers exposed to 5–20 ppm (15–60 mg/m³) DMF (and other solvents), ranging from a few weeks to 4 years. Redlich et al. (1990) carried out biopsies of liver from workers heavily exposed to DMF (and other solvents; quantitative data not reported). Workers exposed for less than 3 months had hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes, and pleomorphic mitochondria. The livers of workers exposed for longer terms (14–120 months) had fatty changes with occasional lipogranuloma.

9.2 Cardiac effects

Excess mortality from ischaemic heart disease in DMF-exposed workers in a US acrylonitrile fibre plant was observed in a historical cohort study (Chen et al., 1988b). Between 1950 and 1982, there were 62 deaths due to ischaemic heart disease (40.3 expected from company rates; $P < 0.01$). The increase was not significant in comparison with the state (South Carolina) rates. A similar observation was made for a second group of 1329 employees at the plant who were potentially exposed to

Concise International Chemical Assessment Document 31

both DMF and acrylonitrile (65 deaths observed, 48.3 expected from company rates; $P < 0.05$). However, the observed number of deaths was not significantly higher than that which would be expected from either state or national rates, possibly due to a “healthy worker effect.” Lifestyle factors such as alcohol and tobacco consumption were suggested to be more likely causes than exposure to DMF, although the specific basis for this contention was not specified (Chen et al., 1988b). The authors noted that South Carolina has a higher ischaemic heart disease mortality rate than the USA.

No convincing evidence of adverse effects on cardiac function was seen in a limited study in which electrocardiographic (ECG) monitoring was carried out on workers at a small synthetic leather plant where DMF was used. Monitoring of eight workers over a workshift revealed possible mild effects (isolated ventricular premature beats after 2 h of work, without “pathological alteration” of the ECG) in one worker (Taccola et al., 1981). In a brief report, ECG changes in workers exposed to DMF were reported (<3 ppm [<9 mg/m³], with peaks up to 1500 ppm [4500 mg/m³], plus skin exposure), but little detail was provided (Kang-De & Hui-Lan, 1981).

Cardiac disturbances, including tachycardia and palpitations, have occasionally been observed in cross-sectional studies of DMF-exposed workers (Lyle, 1979; Lyle et al., 1979; Kang-De & Hui-Lan, 1981; Cirla et al., 1984; Fiorito et al., 1997). Sometimes, the palpitations followed alcohol ingestion (Lyle, 1979; Lyle et al., 1979; Fiorito et al., 1997).

9.3 Cancer

Data on the incidence or mortality of cancer associated with exposure to DMF are limited to case reports of testicular tumours and single well conducted and reported cohort and case-control studies of occupationally exposed populations (Chen et al., 1988a; Walrath et al., 1989). In the cohort study of 3859 actively employed workers with potential exposure to DMF and to DMF and acrylonitrile in an acrylonitrile fibre production facility, the incidences of cancer of the buccal cavity/pharynx, lung, prostate, stomach, nervous system, and bladder were considered in relation to level of and, for some tumours, duration of exposure and were compared with company and national rates. Level of exposure was classified as low (approximately <10 ppm [<30 mg/m³]), moderate (sometimes above 10 ppm [30 mg/m³]), or high, although quantitative data were not reported (Chen et al., 1988a). In an additional case-control study, cancers of the buccal cavity/pharynx ($n = 39$), liver ($n = 6$), prostate ($n = 43$), and testis ($n = 11$) and

malignant melanoma of the skin ($n = 39$) were examined in approximately 8700 workers from four plants, which included a DMF production plant, two acrylic fibre plants that used DMF as a spinning solvent, and a plant using the chemical as a solvent for inks (Walrath et al., 1989).

Three cases of testicular germ cell tumours that occurred during 1981–1983 among 153 white men who repaired the exterior surfaces and electrical components of F4 Phantom jets in the USA were reported by Ducatman et al. (1986), which led to surveys of two other repair shops at different locations, one in which F4 Phantom jets were repaired and one where other types of aircraft were repaired. Four of 680 workers in the F4 Phantom shop had testicular germ cell cancers (approximately one expected) diagnosed during 1970–1983. No cases were reported in the other facility. All seven men had long histories in aircraft repair; although there were many common exposures to solvents in the three facilities, the only one identified as unique to the F4 Phantom jet aircraft repair facilities was to a solvent mixture containing 80% DMF (20% unspecified). Three of the cases had been exposed to this mixture with certainty, and three had probably been exposed. Of the seven cases, five were seminomas and two were embryonal cell carcinomas.

Levin et al. (1987) and Frumin et al. (1989) reported three cases of embryonal cell carcinoma of the testis in workers at one leather tannery in the USA, where it was reported that DMF as well as a wide range of dyes and solvents were used, including such testicular toxins as 2-ethoxyethanol and 2-ethoxyethanol acetate. The latency period ranged from 8 to 14 years. No additional cancers were reported in a screening effort undertaken to identify additional testicular cancers in 51 of the 83 workers at the leather tannery where the three cases were reported (Calvert et al., 1990).

In an investigation of cancer incidence at a plant producing acrylonitrile fibres, compared with company and national rates, there was no increase in the incidence of testicular cancer in 2530 actively employed workers exposed to DMF only. When the data from this cohort were grouped with data from 1329 workers exposed to both DMF and acrylonitrile, there was only one case of testicular cancer, versus 1.7 expected (confidence interval [CI] not reported) (Chen et al., 1988a).

There was no increase in cancer of testis (odds ratio = 0.91; 95% CI = 0.1–8.6; observed number of cases = 11) in the case-control study described above in which the cases were drawn from a population of

N,N-Dimethylformamide

approximately 8700 workers involved in production or use of DMF at four plants (Walrath et al., 1989, 1990). For each case, two controls were selected, matched for age, sex, payroll class, and plant. Potential exposure to DMF was classified as low or moderate based on job title/work area combinations and monitoring data.

Chen et al. (1988a) observed a significant increase in prostate cancer (10 observed vs. 5.1 expected from company rates and 5.2 expected from national rates; $P < 0.10$ for both comparisons) in the 3859 workers exposed either to DMF or to both DMF and acrylonitrile. However, when only DMF-exposed workers (2530) were considered, the standardized incidence rate (SIR) (4 observed vs. 2.4 expected from company rates) was not significant. The odds ratio for prostate cancer in the case-control study of the 8700 DMF-exposed workers from four plants was not significantly elevated (1.48; 95% CI = 0.59–3.74; 43 cases) (Walrath et al., 1989, 1990). When analyses were carried out separately for each of the four plants, an increased incidence was observed only at one plant, where the exposure to DMF was lower and the number of cases was fewer than at the other plants. Adjustment for assumed latency period did not alter the odds ratio. There was no relationship with duration of exposure.

Chen et al. (1988a) also reported a significant increase of cancer of the buccal cavity/pharynx (9 observed vs. 1.6 expected from company rates; $P < 0.10$) in the 2530 DMF-exposed workers (confidence intervals not reported). When combined with data from 1329 workers exposed to both DMF and acrylonitrile, the increase (11 observed) was significant when compared with the company rate (3.2 expected; $P < 0.01$), but not compared with the national rate (6.6 expected). There was no relation to either level or duration of exposure. All cases were heavy, long-term smokers. There was no increase in risk of cancer of the buccal cavity/pharynx in the case-control study of workers at the four plants mentioned above (odds ratio = 0.89; 90% CI = 0.35–2.29; 39 cases) (Walrath et al., 1989, 1990).

9.4 Genotoxicity

Seven studies were identified in which the genotoxicity of DMF in humans has been examined. Four of these studies were critically reviewed by IARC (1999) and were described therein as follows.

Berger et al. (1985) reported that the prevalence of CAs was higher in the blood lymphocytes of 20 workers exposed to DMF, NMF, and dimethylamine than in 18 unexposed workers at the same factory (1.4% vs. 0.4%;

statistical significance not provided). The mean concentrations 1 year prior to blood sampling were 12.3 mg/m³ for DMF, 5.3 mg/m³ for NMF, and 0.63 mg/m³ for dimethylamine. However, the control group had an unusually low level of chromosome breaks. The IARC Working Group noted that the possible effect of smoking was not addressed.

A higher incidence of CAs was observed in the lymphocytes of about 40 workers exposed to DMF than in an unspecified control group (2.74–3.82% vs. 1.10–1.61%; $P < 0.05$). The range of exposure to DMF was 150–180 mg/m³. Workers were also exposed to trace amounts of MEK, butyl acetate, toluene, cyclohexanone, and xylene. After technological improvements designed to reduce DMF exposure levels (range 35–50 mg/m³), the frequency of aberrant cells decreased to 1.49–1.59% (Koudela & Spazier, 1981).

Although Sram et al. (1985) reported in an abstract that there was no evidence of increased frequency of CA in peripheral lymphocytes in workers exposed to DMF, no details were provided.

Seiji et al. (1992) reported that the mean SCE rate was higher in the blood cells of 22 women exposed to three concentrations of DMF (0.3–5.8 ppm [0.9–17.4 mg/m³]) in a leather production factory than in 22 unexposed controls from the same factory, matched by sex, age, and residence. None of the women smoked tobacco or drank alcohol. The incidence of SCEs was significantly increased in a dose-related manner in the mid- and high-exposure groups.

Based on review of these studies, IARC (1999) concluded that “The positive data for cytogenetic damage in humans occupationally exposed to it are not very convincing.”

Three relevant reports, including one for which only an abstract was identified in which few details were provided (Haber et al., 1990), were identified in addition to those reviewed by IARC (1999). The two investigations for which reporting was adequate are described here.

Major et al. (1998) reported that for workers with 3–10 years of occupational exposure to undefined levels of DMF and/or acrylonitrile, the prevalence of peripheral lymphocytes with CAs was increased compared with unexposed controls (see below). After a further 7 months of exposure (to DMF at 0.2–8 ppm [0.6–24 mg/m³] and to acrylonitrile at 0–17.6 mg/m³), the incidence in the exposed group increased to 5.1% but did not increase further up to 20 months. The incidence of SCEs was also

Concise International Chemical Assessment Document 31

higher than control values at the start of the 20-month study and remained higher at 7 and 20 months. The UDS level was similar to that in controls when the study started, but had increased in the exposed group by month 7. In addition to concomitant exposure to acrylonitrile, current smoking was also a confounding factor, with CA and SCE yields being significantly higher in exposed smokers than in exposed non-smokers. Nevertheless, CA yields at 7 months were significantly higher in exposed non-smokers than in control non-smokers and in exposed smokers than in control smokers.

Cheng et al. (1999) measured SCE frequency in peripheral lymphocytes of workers at a resin synthesis plant. Nine workers had low exposure (median 5.2 ppm [15.6 mg/m³]; range 0.9–5.3 ppm [2.7–15.9 mg/m³]), and 20 workers had high exposure (median 24.8 ppm [74.4 mg/m³]; range 11.4–83.3 ppm [34.2–249.9 mg/m³]). There were no differences between the two groups; there was no additional control population.

Results of studies on genotoxicity conducted since the IARC evaluation have not contributed materially to the database, which was considered by IARC (1999) not to provide convincing evidence. Certainly, the results, when taken as a whole, are inconsistent and not readily explained by variations in exposure.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

DMF has been the focus of several toxicity studies conducted on a range of species. The most sensitive end-points for terrestrial and aquatic organisms are presented below and are summarized in Table 5.

10.1 Aquatic environment

A number of studies are available for a range of taxa, including protozoa, blue-green algae, diatoms, green algae, macrophytes, molluscs, oligochaetes, crustaceans, insect larvae, and fish.

For four species of fish, EC₅₀ and LC₅₀ values ranged from approximately 7100 to 12 000 mg/litre (Batchelder, 1976; Johnson & Finley, 1980; Call et al., 1983; Poirier et al., 1986; Groth et al., 1994). The most sensitive fish species appears to be the bluegill (*Lepomis macrochirus*), with an LC₅₀ of 7100–7500 mg/litre.

Aquatic invertebrates tested include the water flea (*Daphnia magna*) and various species of insect larvae.

The water flea appears to be the most sensitive invertebrate, with a NOEL of 1140 mg/litre. Acute end-points (EC₅₀ and LC₅₀) for *Daphnia magna* range from 12 400 to 15 700 mg/litre, whereas chronic studies provide end-points for mortality between 1140 and 3721 mg/litre (Call et al., 1983; Leblanc & Surprenant, 1983; Adams & Heidolph, 1985; Poirier et al., 1986; Ziegenfuss et al., 1986; Sebaugh et al., 1991). The 48-h LC₅₀s obtained for various species of insect larvae were much higher and ranged from 33 500 to 36 200 mg/litre (Call et al., 1983; Poirier et al., 1986; Ziegenfuss et al., 1986).

The most sensitive alga appears to be *Selenastrum capricornutum*, with a 14-day NOEC value for growth inhibition of 480 mg/litre (Hughes & Vilkas, 1983). Results for two other green algae range from 8900 to 10 000 mg/litre (Stratton & Smith, 1988; El Jay, 1996). Peterson et al. (1997) obtained an IC₂₅ for growth inhibition of 6200 mg/litre for the diatom *Nitzschia* sp. In the same study, blue-green algae appeared to be the least sensitive, with IC₂₅s for growth inhibition ranging from 7000 to 15 100 mg/litre for three tested species (Peterson et al., 1997), a finding that differs from earlier data (Stratton, 1987). Because of the high degree of quality assurance/quality control associated with the Peterson et al. (1997) study, these data are considered as definitive levels of toxicity to blue-green algae.

Rajini et al. (1989) measured the lethal response of the ciliated protozoan *Paramecium caudatum* to acute (10-min and 4-h) exposures to DMF. The 4-h LC₅₀ was found to be 20 465 mg/litre. A recent paper reports EC₅₀s of 8190–9870 mg/litre for deformations and LC₅₀s of 19 700–31 700 mg/litre for the protozoan *Spirostomum ambiguum* (Nalecz-Jawecki & Sawicki, 1999).

Marine organisms tested include the bacteria *Vibrio fischeri*, the common shrimp (*Crangon crangon*), and a fish, the winter flounder (*Pleuronectes americanus*). For the decrease in luminescence in *Vibrio fischeri*, the 5-min EC₅₀ value of 20 000 mg/litre (Curtis et al., 1982) is in the same order of magnitude as the values (13 260–14 830 mg/litre) obtained by Harwood¹ with a 15-min exposure. IC₂₅ values calculated by Harwood¹ with the same data set range from 5830 to 6730 mg/litre.

¹ Personal communications from M. Harwood, Environment Canada, to A. Chevrier, Environment Canada, dated 2 and 5 December 1997.

N,N*-Dimethylformamide*Table 5: Toxicity of DMF to various organisms.**

Test species	Latin name	End-point	Range	References
Bacteria	<i>Vibrio fischeri</i>	5-min EC ₅₀ light production	20 000 mg/litre	Curtis et al. (1982)
Bacteria	<i>Vibrio fischeri</i>	15-min IC ₅₀ light inhibition 15-min IC ₂₅ light inhibition	13 260–14 830 mg/litre 5830–6730 mg/litre	Harwood ^a
Protozoan	<i>Paramecium caudatum</i>	4-h LC ₅₀ mortality	20 465 mg/litre	Rajini et al. (1989)
Protozoan	<i>Spirostomum ambiguum</i>	24-h EC ₅₀ deformations 24-h LC ₅₀ mortality 48-h EC ₅₀ deformations 48-h LC ₅₀ mortality	9870 mg/litre 31 700 mg/litre 8190 mg/litre 19 700 mg/litre	Nalecz-Jawecki & Sawicki (1999)
Blue-green algae	<i>Nostoc</i> sp.	10- to 14-day EC ₅₀ growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	<i>Anabaena</i> sp.	10- to 14-day EC ₅₀ growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	<i>Anabaena cylindrica</i>	10- to 14-day EC ₅₀ growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	<i>Anabaena variabilis</i>	10- to 14-day EC ₅₀ growth inhibition test	<480 mg/litre	Stratton (1987)
Blue-green algae	<i>Anabaena inaequalis</i>	10- to 14-day EC ₅₀ growth inhibition test	5700 mg/litre	Stratton (1987)
Blue-green algae	<i>Anabaena flos-aquae</i>	48-h IC ₂₅ growth inhibition	15 100 mg/litre	Peterson et al. (1997)
Blue-green algae	<i>Microcystis aeruginosa</i>	48-h IC ₂₅ growth inhibition	7000 mg/litre	Peterson et al. (1997)
Blue-green algae	<i>Oscillatoria</i> sp.	48-h IC ₂₅ growth inhibition	10 400 mg/litre	Peterson et al. (1997)
Diatom	<i>Nitzschia</i> sp.	48-h IC ₂₅ growth inhibition	6200 mg/litre	Peterson et al (1997)
Green algae	<i>Selenastrum capricornutum</i>	48-h IC ₂₅ growth inhibition	7700 mg/litre	Peterson et al. (1997)
Green algae	<i>Selenastrum capricornutum</i>	72-h IC ₂₅ growth as cell numbers	3420–6280 mg/litre	Harwood ^a
Green algae	<i>Selenastrum capricornutum</i>	growth at day 4	inhibition at 5000 mg/litre	El Jay (1996)
Green algae	<i>Selenastrum capricornutum</i>	growth inhibition NOEC	480 mg/litre	Hughes & Vilkas (1983)
Green algae	<i>Selenastrum capricornutum</i>	growth at day 4	stimulation at 1000 mg/litre	El Jay (1996)
Green algae	<i>Chlorella vulgaris</i>	growth at day 4	inhibition at 10 000 mg/litre	El Jay (1996)
Green algae	<i>Chlorella vulgaris</i>	growth at day 4	stimulation at 1000 mg/litre	El Jay (1996)
Green algae	<i>Chlorella pyrenoidosa</i>	10- to 14-day EC ₅₀ reduction in growth	8900 mg/litre	Stratton & Smith (1988)
Duckweed	<i>Lemna minor</i>	7-day IC ₂₅ growth inhibition	4900 mg/litre	Peterson et al. (1997)
Water flea	<i>Daphnia magna</i>	acute 48-h EC ₅₀ immobilization	14 500 mg/litre	Poirier et al. (1986)
Water flea	<i>Daphnia magna</i>	acute 48-h EC ₅₀ survival and mortality	15 700 mg/litre	Adams & Heidolph (1985)
Water flea	<i>Daphnia magna</i>	acute 48-h LC ₅₀ mortality	14 400 mg/litre	Ziegenfuss et al. (1986)
Water flea	<i>Daphnia magna</i>	acute 48-h LC ₅₀ mortality	14 530 mg/litre	Call et al. (1983)
Water flea	<i>Daphnia magna</i>	acute 48-h EC ₅₀ immobilization	13 100 mg/litre	Sebaugh et al. (1991)

Concise International Chemical Assessment Document 31**Table 5 (contd).**

Test species	Latin name	End-point	Range	References
Water flea	<i>Daphnia magna</i>	chronic 21-day EC ₅₀ survival and mortality	3721 mg/litre	Adams & Heidolph (1985)
Water flea	<i>Daphnia magna</i>	chronic 21-day NOEL/LOEC survival and mortality	1500–3000 mg/litre	Adams & Heidolph (1985)
Water flea	<i>Daphnia magna</i>	chronic 28-day NOEL survival and mortality	1140 mg/litre	Leblanc & Surprenant (1983)
Water flea	<i>Daphnia magna</i>	acute 48-h EC ₅₀ survival and mortality	12 400 mg/litre	Leblanc & Surprenant (1983)
Insect larvae	<i>Paratanytarsus parthenogeneticus</i>	48-h EC ₅₀	36 200 mg/litre	Poirier et al. (1986)
Insect larvae	<i>Tanytarsus dissimilis</i>	48-h LC ₅₀	36 000 mg/litre	Call et al. (1983)
Insect larvae	<i>Chironomus tentans</i>	acute 48-h LC ₅₀ mortality	33 500 mg/litre	Ziegenfuss et al. (1986)
Shrimp	<i>Crangon crangon</i>	LC ₅₀	>100 mg/litre	Portmann & Wilson (1971)
Rainbow trout	<i>Oncorhynchus mykiss</i>	acute 96-h LC ₅₀ mortality	9800–12 000 mg/litre	Johnson & Finley (1980); Call et al. (1983); Poirier et al. (1986)
Winter flounder	<i>Pleuronectes americanus</i>	inhibition of the enzyme activity in intestinal mucosae	50 000 mg/litre	Janicki & Kinter (1971)
Zebrafish	<i>Brachydanio rerio</i>	acute 96-h LC ₅₀ mortality	8840 mg/litre	Groth et al. (1994)
Fathead minnow	<i>Pimephales promelas</i>	acute 96-h LC ₅₀ mortality	9080–11 400 mg/litre	Batchelder (1976); Call et al. (1983); Poirier et al. (1986)
Bluegill	<i>Lepomis macrochirus</i>	acute 96-h LC ₅₀ mortality	7100–7500 mg/litre	Call et al. (1983); Poirier et al. (1986)
Soil fungi	<i>Sclerotinia homeocarpa</i>	EC ₅₀ inhibition of fungal growth, compared with a control growth of 50–70 mm	4840 mg/litre	Stratton (1985)
Soil fungi	<i>Pythium ultimum</i>	EC ₅₀ inhibition of fungal growth, compared with a control growth of 50–70 mm	10 250 mg/litre	Stratton (1985)
Soil fungi	<i>Pestalotia</i> sp.	EC ₅₀ inhibition of fungal growth, compared with a control growth of 50–70 mm	5970 mg/litre	Stratton (1985)
Wheat and bean seeds		inhibition of germination	50 000 mg/litre	Szabo (1972)
Rat		2-year inhalational NOEL, 6 h/day, 5 days/week exposure changes in body weight and clinical chemistry parameters	75 mg/m ³	Malley et al. (1994)

^a Personal communications from M. Harwood, Environment Canada, to A. Chevrier, Environment Canada, dated 2 and 5 December 1997.

Portmann & Wilson (1971) reported an LC₅₀ of >100 mg/litre for *Crangon crangon*.

10.2 Terrestrial environment

There is little information available on the toxicity of DMF to terrestrial vascular plants. Szabo (1972) reported that DMF did not inhibit germination of wheat

and bean seeds at 1% (approximately 10 000 mg/litre), but did at 5% (approximately 50 000 mg/litre); however, little methodological information is provided with which to assess the quality of the data. The IC₂₅ of 4900 mg/litre for the duckweed (*Lemna minor*), an aquatic angiosperm, indicates that terrestrial angiosperms may not be sensitive to DMF (Peterson et al., 1997). The most sensitive organism in the terrestrial

compartment appears to be the soil fungus *Sclerotinia homeocarpa*, with an EC₅₀ of 4840 mg/litre for growth inhibition (Stratton, 1985).

Although information on effects of DMF on wild-life has not been identified, a review of laboratory studies on experimental animals (WHO, 1991) concludes that acute toxicity of DMF in a variety of species is low. Only one chronic (2-year) inhalation assay was identified in recent literature (Malley et al., 1994). In that study, a LOEC of 25 ppm (75 mg/m³) following inhalation of DMF was reported, based on changes in body weight and clinical chemistry.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

11.1.1.1 Effects in humans

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with gastrointestinal disturbance, alcohol intolerance, increases in serum hepatic enzymes (AST, ALT, (–GT, and AP), and histopathological effects (hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes, pleomorphic mitochondria, and fatty changes with occasional lipogranuloma) being observed. Effects observed at lowest concentrations in cross-sectional studies in occupationally exposed populations for which there is some information on dose–response are increases in serum hepatic enzymes.

Based on the limited data available, there is no convincing, consistent evidence of increased risk of cancer at any site associated with exposure to DMF in the occupational environment. Case reports of testicular cancers have not been confirmed in a cohort and case–control study. There have been no consistent increases in tumours at other sites associated with exposure to DMF.

There is also little consistent, convincing evidence of genotoxicity in populations occupationally exposed to DMF, with results of available studies of exposed workers (to DMF and other compounds) being mixed. The pattern of observations is not consistent with variations in exposure across studies. However, in view

of the positive dose–response relationship observed in the one study in which it was investigated, this area may be worthy of additional work, although available data on genotoxicity in experimental systems are overwhelmingly negative.

11.1.1.2 Effects in experimental animals

DMF has low acute toxicity and is slightly to moderately irritating to the eyes and skin, based on limited data acquired in non-standard assays. Available data are inadequate as a basis for characterization of the potential of DMF to induce sensitization. In acute and repeated-dose toxicity studies, DMF has been consistently hepatotoxic, inducing effects on the liver at lowest concentrations or doses. The profile of effects includes alterations in hepatic enzymes, increases in liver weight, progressive degenerative histopathological changes and eventually cell death, and increases in serum hepatic enzymes. Species variation in sensitivity to these effects has been observed, with the order of sensitivity being mice > rats > monkeys.

Although the database for carcinogenicity is limited to two adequately conducted bioassays in rats and mice, there have been no increases in the incidence of tumours following chronic inhalation exposure to DMF. The weight of evidence for genotoxicity is overwhelmingly negative, based on extensive investigation in *in vitro* assays, particularly for gene mutation, and a more limited database *in vivo*.

DMF has induced adverse reproductive effects only at concentrations considerably greater than those associated with adverse effects on the liver. In adequately conducted and reported primarily recent developmental studies, fetotoxic and teratogenic effects have been consistently observed only at maternally toxic concentrations or doses.

Available data are inadequate as a basis for assessment of the neurological, immunological, or skin sensitizing effects of DMF.

The following guidance is provided as a possible basis for derivation of limits of exposure and judgement of the quality of environmental media by relevant authorities.

11.1.2 Criteria for setting tolerable concentrations or guidance values

In both humans and experimental animals exposed to DMF, the target organ has been the liver, consistent with local action of a reactive intermediate in the tissue where it is primarily metabolized. Available data indicate that there are considerable variations between experimental animals and humans in the proportion of

Concise International Chemical Assessment Document 31

DMF metabolized by the putatively toxic pathway, with the resulting implication that humans may be more sensitive to the effects of DMF. Also, since there are data available to serve as the basis for at least crude characterization of exposure–response for parameters associated with hepatic toxicity in workers, the tolerable concentration (TC) is based on data on inhalation in humans, although it should be noted that these values do not account for likely additional exposure by dermal absorption. Analyses of dose–response for hepatic effects in the studies in experimental animals are presented for comparison. Since exposure in the general environment is likely to be primarily through air, emphasis in this section is on the generally more extensive database on toxicity by the inhalation route.

Effects on the liver observed at lowest concentration in cross-sectional studies in occupationally exposed populations for which there is some information on exposure–response are increases in serum hepatic enzymes. The results concerning exposure–response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations in the range of 1–6 ppm (3–18 mg/m³). At higher levels of exposure (>7 ppm [>21 mg/m³]), increased serum levels of hepatic enzymes have been observed consistently. Cirila et al. (1984) reported significant increases in serum (–GT in 100 workers exposed to 7 ppm (21 mg/m³). Similarly, Fiorito et al. (1997) reported significant increases in serum ALT, AST, (–GT, and AP in workers exposed to 7 ppm (21 mg/m³).

Catenacci et al. (1984) did not observe differences between serum levels of SGOT, SGPT, and (–GT in workers employed for more than 5 years. In view of the small number of subjects exposed to the mean TWA of 6 ppm (18 mg/m³) DMF (*n* = 28), negative results reported therein may be a function of lack of power of the study to detect a meaningful effect and are not, therefore, necessarily inconsistent with the results of Cirila et al. (1984) and Fiorito et al. (1997).

Based on the lowest-observed-adverse-effect level (LOAEL) of 7 ppm (21 mg/m³), a TC¹ has been derived as follows:

$$\begin{aligned} \text{TC} &= \frac{7\text{ppm}}{50} \times 8/24 \times 5/7 \\ &= 0.03 \text{ ppm (0.1 mg/m}^3\text{)} \end{aligned}$$

¹ The term “tolerable concentration” is used here in the same sense as the term “tolerable intake” as defined by IPCS (1994), i.e., “an estimate of the intake of a substance over a lifetime that is considered to be without appreciable health risk.”

where:

- 7 ppm (21 mg/m³) is the LOAEL for increases in serum hepatic enzymes in workers exposed primarily to DMF, reported by Cirila et al. (1984) and Fiorito et al. (1997); it should be noted that the observed small increases in a few serum hepatic enzymes are considered to be only minimally adverse, with associated hepatic damage likely being reversible upon cessation of exposure;
- 8/24 and 5/7 are the factors to convert exposure during 8 h/day and 5 days/week, respectively, to continuous exposure;
- 50 is the uncertainty factor (×10 for intraspecies [interindividual]² variation, including sensitive subgroups; ×5 to account primarily for less than lifetime exposure; although the TC is based on a LOAEL, observed effects are considered to be only minimally adverse).

Although not the basis of the TC developed here, there are several important observations from dose–response analyses of the results of the studies in animals (see Appendix 4). The lowest reported benchmarks for a range of hepatic effects in rats and mice following inhalation are those for histopathological lesions in the liver of both rats and mice, which are higher but in the same range as those reported to induce effects on hepatic function in the studies in workers. It should be noted, though, that, due to the nature of the effects on which they were based (increases in serum hepatic enzymes versus histological effects), the benchmarks in humans are not strictly comparable.

It is also evident that there is progression of effects from the medium-term to long-term studies, with effects being more severe following long-term exposure (although quantitative values for the lowest benchmarks for different types of lesions in the medium-term and long-term studies are similar).

11.1.3 Sample risk characterization

Due to the nature of use, patterns of release, and environmental fate of DMF, the focus of the human health risk characterization for indirect exposure is populations exposed through air in the vicinity of industrial point sources.

With a reported annual loading of less than 20 tonnes and generally less than 1 tonne at any location in the sample country (i.e., Canada), continuous releases of consistent magnitude likely result in long-term expo-

² Available quantitative data are insufficient to replace default values for the component of this uncertainty factor with data-derived values (IPCS, 1994).

sure to small concentrations (worst-case estimate in Canada, 0.11 mg/m^3) of DMF near point sources. Because of the absence of empirical data on concentrations of DMF in air in Canada, an estimated exposure value (EEV) was calculated based on release data for the largest Canadian emitter, making several conservative assumptions.

The largest annual release reported at one location can be expressed on a daily basis ($12.7 \text{ tonnes/year} = 0.0348 \text{ tonnes/day}$ or $3.48 \times 10^7 \text{ mg/day}$). As a conservative estimate, it will be assumed that daily releases of DMF are contained within a cylinder having a radius of 1 km centred on the point source. Dispersion within 1 km is likely a conservative assumption for a number of reasons. First, the greatest reported emissions are occurring in a mixed industrial and agricultural area (Environment Canada, 1999b). The site is paved with asphalt; as such, wild plants and mammals will not likely be found in the immediate vicinity of the source. Finally, although the specific dispersal behaviour of DMF has not been documented near the source, results of dispersion modelling indicate that concentrations of other contaminants released to air elsewhere tend to decrease rapidly within a few kilometres of industrial point sources (e.g., Davis, 1997; Thé, 1998).

Upward movement of organic compounds generally does not exceed 100 m at night and may exceed 1000 m during the day.¹ The more conservative value of 100 m will be used as a ceiling for estimating the exposure concentrations throughout the day.

This provides a dispersal volume of $3.14 \times 10^8 \text{ m}^3$ in the form of a cylinder 100 m in height and 1 km in radius. With a daily release of $3.48 \times 10^7 \text{ mg/day}$, the daily increase in the concentration of DMF in air is estimated at 0.11 mg/m^3 . Since ambient levels in the cylinder are likely to be lower than this daily increase of 0.11 mg/m^3 , it will be used as a conservative EEV. Reaction with hydroxyl radicals will tend to reduce the concentrations of DMF in the daytime. Since the degradation half-life of DMF could be a week or more, continuous daily inputs would lead to buildup of DMF within the cylinder in the absence of any other loss process. However, fugacity-based modelling suggests that advection processes, i.e., rain and wind, are the major factors in determining concentrations in the atmosphere. Even under essentially stagnant conditions, with a wind speed of 1 km/h, the rate of advection of DMF out of the cylinder is so fast that the steady-state concentration would be 0.01 mg/m^3 or less. At a typical average wind speed of 10 km/h, the concentration of DMF in the cylinder would be

reduced by a factor of approximately 100. The EEV of 0.11 mg/m^3 is generally higher than or comparable to measurements made in other countries.

Worst-case estimates of airborne levels in the immediate vicinity of the largest emitter in the sample country (0.11 mg/m^3), which are likely 10- to 100-fold greater than those anticipated under most conditions, do not appreciably exceed the TC (0.1 mg/m^3) derived on the basis of increases in serum hepatic enzymes in exposed workers.

11.1.4 Uncertainties and degree of confidence in human health risk characterization

Quantitative estimates of ambient levels of DMF in the vicinity of point sources in the sample country on which the human health risk characterization is based are highly uncertain (see discussion of uncertainty in section 11.2.3) and likely conservative, although consistent with highest concentrations measured in other countries. The proximity of these predicted concentrations in the vicinity of point sources to residential areas is also unknown. Available monitoring data are inadequate as a basis for characterization of the exposure of the general population to DMF.

There is a high degree of confidence based on studies in both humans and experimental animals that the liver is the target organ for the toxicity of DMF. Cross-sectional studies on hepatic effects in workers, limited principally to males, were complicated by co-exposures to other substances and limitations of available data on exposure, including, in some cases, lack of monitoring data for individuals. However, the levels that induced minimally adverse effects were remarkably consistent across a large number of studies. The TC developed on the basis of increases in serum hepatic enzymes in occupationally exposed populations is likely conservative, since it does not take into account additional exposure by the dermal route.

Although cases of testicular cancer among people exposed to DMF have been reported, these findings have not been corroborated in (limited) epidemiological studies, and it is thus unlikely that DMF is carcinogenic to humans.

11.2 Evaluation of environmental effects

11.2.1 Terrestrial assessment end-points

Since most DMF appears to be released to air in the sample country, and based on the fate of DMF in the ambient environment, biota are expected to be exposed to DMF primarily in air; little exposure to DMF from surface water, soil, or benthic organisms is expected. Based on this, and because of the low toxicity of DMF to

¹ Notes from N.J. Bunce, University of Guelph, Guelph, Ontario, to A. Chevrier, Environment Canada, dated 1 June 1998.

Concise International Chemical Assessment Document 31

a wide range of aquatic and soil organisms, it is unlikely that organisms will be exposed to harmful levels of DMF in Canadian surface waters, soils, or groundwater.

Therefore, the focus of the environmental risk characterization will be on terrestrial organisms exposed directly to DMF in ambient air.

Terrestrial plants can be exposed to DMF by direct contact with the atmosphere, but also conceivably by diffusion from raindrops deposited on leaves. No data are available on the toxicity of DMF to terrestrial vascular plants. Seeds, soil fungi, and aquatic angiosperm macrophytes can be used as indicators of the potential sensitivities of trees, shrubs, and other plants. The most sensitive of these organisms appears to be the soil fungus *Sclerotinia homeocarpa*, with an EC_{50} of 4840 mg/litre for growth inhibition (Stratton, 1985). In view of the generally high effect concentrations, it is unlikely that terrestrial plants are particularly sensitive to DMF.

As most DMF is released to air and bioaccumulation is not expected, effects on wildlife will occur mainly through direct exposure by inhalation in the vicinity of the point source. Based on the available information, the home range of common small to medium-sized eastern Canadian mammals is generally much less than 1 km² (Banfield, 1974; Burt & Grossenheider, 1976; Forsyth, 1985; US EPA, 1999). By contrast, the home range of the raccoon, a common suburban visitor, is quite variable in size, reportedly ranging from a few square kilometres to thousands of square kilometres (Burt & Grossenheider, 1976; US EPA, 1999). Therefore, small mammals are likely exposed over long periods to highest concentrations of DMF within a few kilometres of the site, while the more mobile medium-sized mammals are probably exposed over time to lower average levels of DMF.

No information has been found on effects of DMF on wildlife. Experimental animals used in laboratory studies will be used as surrogates for small and medium-sized mammals exposed to DMF through inhalation.

11.2.2 Sample environmental risk characterization

The calculation of the EEV is presented in section 11.1.3.

Analysis of exposure pathways and subsequent identification of sensitive receptors are the basis for selection of environmental assessment end-points (e.g., adverse reproductive effects on sensitive fish species in a community). For each end-point, a conservative EEV is selected and an estimated no-effects value (ENEV) is determined by dividing a critical toxicity value (CTV) by an application factor. A hyperconservative or conservative quotient (EEV/ENEV) is calculated for each

of the assessment end-points in order to determine whether there is potential ecological risk.

The long-term (18-month) inhalation LOAEC of 75 mg/m³ measured for mice is used as a CTV for exposure of small mammals. This value was selected from a large data set composed of acute and long-term studies conducted on a number of laboratory species. Although no direct effects related to survival were observed at the exposure concentrations (up to 1200 mg/m³), nor were any haematological changes or effects on the estrous cycle observed, the incidence of hepatocellular hypertrophy, hepatic single-cell necrosis, and hepatic Kupffer cell hyperplasia/pigment accumulation was increased at 75 mg/m³ (Malley et al., 1994). Such effects may not directly manifest themselves as population-level effects in wildlife species; therefore, the ENEV is derived by dividing the CTV by a reduced application factor of 5. This factor also accounts for the extrapolation from a low-effect level to a no-effect level, as well as the uncertainty surrounding the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 15 mg/m³. Therefore, using the EEV of 0.11 mg/m³, the quotient EEV/ENEV = 0.007. Since this conservative quotient is less than 1, it is unlikely that DMF causes adverse effects on terrestrial organisms in the sample country.

11.2.3 Discussion of uncertainty

There are a number of potential sources of uncertainty in this environmental risk assessment.

The calculated Henry's law constant is uncertain, as solubility cannot be measured. Based on sensitivity analysis, the fugacity-based partitioning estimates can be sensitive to the value used as the Henry's law constant.¹

Ambient levels near Canadian sources are not available. The EEV was therefore estimated based on available information on releases. This calculated EEV is, however, generally consistent with the highest concentrations measured in other countries. It is unlikely that there are concentrations of DMF in the sample country that are higher than those calculated and used in this assessment. For air, reported releases at the selected location by far exceed reported releases to air at any other location and as such likely constitute a worst-case scenario. For water, concentrations are expected to

¹ Collection of notes and modelling results submitted by A. Bobra, AMBEC Environmental Consultant, to Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, 1999.

be low because of the limited releases identified to this medium and the limited partitioning of DMF from air into water. Small spills and leakage could increase levels of DMF in soil and groundwater; however, the available information suggests that such releases would be small and infrequent.

Regarding effects of DMF on terrestrial organisms, although no toxicity data were identified for vascular plants, data for effects on seeds and aquatic macrophytes suggest that terrestrial vegetation is not particularly sensitive to DMF. Additional evidence of effects on terrestrial plants would strengthen the conclusion that DMF is not expected to damage gymnosperms, angiosperms, and other vascular plants.

There is uncertainty concerning the extrapolation from available toxicity data for laboratory mammals to potential effects on wildlife populations. To account for these uncertainties, an application factor was used in the environmental risk analysis to derive ENEVs.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC (1999) has classified DMF in Group 3 (not classifiable as to its carcinogenicity to humans). There was inadequate evidence for carcinogenicity of DMF in humans. There was evidence suggesting lack of carcinogenicity of DMF in experimental animals.

Concise International Chemical Assessment Document 31

REFERENCES

- Adams WJ, Heidolph BB (1985) Short-cut chronic toxicity estimates using *Daphnia magna*. In: Cardwell RD, Purdy R, Bahner RC, eds. *Aquatic toxicity and hazard assessment: seventh symposium* Philadelphia, PA, American Society for Testing and Materials, pp. 87–103 (ASTM Special Technical Publication 854).
- Agrelo C, Amos H (1981) DNA repair in human fibroblasts. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 528–532 (Progress in Mutation Research, Vol. 1).
- Amster MB, Hijazi N, Chan R (1983) Real time monitoring of low level air contaminants from hazardous waste sites. In: *National Conference on Management of Uncontrolled Hazardous Waste Sites*, 31 October – 2 November 1983, Washington, DC. Silver Spring, MD, Hazardous Materials Control Research Institute/Consultants, pp. 98–99.
- Angerer J, Göen T, Krämer A, Kafferlein HU (1998) *N*-Methyl-carbamoyl adducts at the *N*-terminal valine of globin in workers exposed to *N,N*-dimethylformamide. *Archives of toxicology*, 72:309–313.
- Antoine JL, Arany J, Léonard A, Henrotte J, Jenar-Dubuisson G, Decat G (1983) Lack of mutagenic activity of dimethylformamide. *Toxicology*, 26:207–212.
- Arena N, Santacruz G, Alia EF, Baldus M, Corgiolu T, Alia EE (1982) [Structural and ultrastructural changes to the myocardium in rabbits exposed to dimethylformamide vapour.] *Bollettino della Societa Italiana di Biologia Sperimentale*, 58:1496–1501 (in Italian).
- Atkinson R (1988) Estimation of gas-phase hydroxyl radical rate constants for organic chemicals. *Environmental toxicology and chemistry*, 7:435–442.
- Baker RSU, Bonin AM (1981) Study of 42 coded compounds with the *Salmonella*/mammalian microsome assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 249–260 (Progress in Mutation Research, Vol. 1).
- Banfield AWF (1974) *The mammals of Canada*. Toronto, Ontario, University of Toronto Press.
- BASF (1984) *13-week oral toxicity (feeding) study with dimethylformamide (DMF) in beagle dogs with cover sheet dated 061289*. BASF Aktiengesellschaft. Washington, DC, US Environmental Protection Agency (TSCA Submission EPA Document No. 86-890000633).
- Batchelder TL (1976) *Evaluation of dimethylformamide in the aquatic environment (final report) (sanitized)*. Washington, DC, US Environmental Protection Agency (EPA No. 86-890001140S).
- Becci PJ, Voss KA, Johnson WD, Gallo MA, Babish JG (1983) Subchronic feeding study of *N,N*-dimethylformamide in rats and mice. *Journal of the American College of Toxicology*, 2:371–378.
- Begert A (1974) Biological purification of dimethylformamide-containing industrial sewage. *Vom Wasser*, 43:403–432.
- Berger H, Haber I, Wünsch G, Bittersohl G (1985) [Epidemiologic studies of exposure to dimethylformamide.] *Zeitschrift für die Gesamte Hygiene und ihre Grenzgebiete*, 31:366–368 (in German) [cited in IARC, 1999].
- Brooks TM, Dean BJ (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay with preincubation. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 261–270 (Progress in Mutation Research, Vol. 1).
- Brugnone F, Perbellini L, Gaffuri E (1980) *N,N*-Dimethylformamide concentration in environmental and alveolar air in an artificial leather factory. *British journal of industrial medicine*, 37:185–188.
- BUA (1994) *N,N*-Dimethylformamide. GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance. Stuttgart, German Chemical Society, Wissenschaftliche Verlagsgesellschaft, December 1991 (BUA Report No. 84).
- Burt WH, Grossenheider RP (1976) *A field guide to the mammals of North America north of Mexico*, 3rd ed. Boston, MA, Houghton Mifflin Company.
- Buylaert W, Calle P, DePaepe P, Verstraete A, Samyn N, Vogelaers D, Vandenbulcke M, Belpaire F (1996) Hepatotoxicity of *N,N*-dimethylformamide (DMF) in acute poisoning with the veterinary euthanasia drug T-61. *Human experimental toxicology*, 15:607–611.
- Cai SX, Huang MY (1979) [Investigation on occupational hazard in a butadiene monomer workshop of a *cis*-butadiene rubber plant.] *Journal of hygiene research*, 8(1):22–49 (in Chinese) [cited in WHO, 1991].
- Cai S-X, Huang M-Y, Xi L-Q, Li Y-L, Qu J-B, Kawai T, Yasugi T, Mizunuma K, Watanabe T, Ikeda M (1992) Occupational dimethylformamide exposure. 3. Health effects of dimethylformamide after occupational exposure at low concentrations. *International archives of occupational and environmental health*, 63:461–468.
- Call DJ, Brooke LT, Ahmad N, Richter JE (1983) *Toxicity and metabolism studies with EPA priority pollutants and related chemicals in freshwater organisms*. Duluth, MN, US Environmental Protection Agency (EPA-600/3-83-095).
- Calvert GM, Fajen JM, Hills BW, Halperin WE (1990) Testicular cancer, dimethylformamide, and leather tanneries. *Lancet*, 336:1253–1254.
- Carter JL, Young DA (1983) Biodegradation of chemical plant wastewater containing dimethylformamide. In: *Proceedings of the 38th Industrial Waste Conference*, 10–12 May 1983. Boston, MA, Butterworth Publishers, pp. 481–486.
- Casal Lareo A, Perbellini L (1995) Biological monitoring of workers exposed to *N,N*-dimethylformamide. II. Dimethylformamide and its metabolites in urine of exposed workers. *International archives of occupational and environmental health*, 67:47–52.
- Catenacci G, Grampella D, Terzi R, Sala A, Pollini G (1984) Hepatic function in subjects exposed to environmental concentrations of DMF lower than the actually proposed TLV. *Giornale Italiano di Medicina del Lavoro*, 6:157–158.
- Chary S (1974) Dimethylformamide: a cause of acute pancreatitis? *Lancet*, ii:356.
- Chen JL, Fayerweather WE, Pell S (1988a) Cancer incidence of workers exposed to dimethylformamide and/or acrylonitrile. *Journal of occupational medicine*, 30:813–818.

N,N-Dimethylformamide

Chen JL, Fayerweather WE, Pell S (1988b) Mortality study of workers exposed to dimethylformamide and/or acrylonitrile. *Journal of occupational medicine*, 30:819–821.

Cheng T, Hwang S, Kuo H, Luo J, Chang M (1999) Exposure to epichlorohydrin and dimethylformamide, glutathione S-transferases and sister chromatid exchange frequencies in peripheral lymphocytes. *Archives of toxicology*, 73(4/5):282–287.

Chieli E, Saviozzi M, Menicagli S, Branca T, Gervasi PG (1995) Hepatotoxicity and P-4502E1-dependent metabolic oxidation of *N,N*-dimethylformamide in rats and mice. *Archives of toxicology*, 69:165–170.

Chivers CP (1978) Disulfiram effect from inhalation of dimethylformamide. *Lancet*, i:331.

Chudoba J, Pitter P, Madera V (1969) Biological oxidation of lower aliphatic amines and dimethylformamide. *Chemicky Prumysl*, 19:76–80.

Cirla AM, Pisati G, Invernizzi E, Torricelli P (1984) Epidemiological study on workers exposed to low dimethylformamide concentrations. *Giornale Italiano di Medicina del Lavoro*, 6:149–156.

CITI (1992) *Biodegradation and bioaccumulation data on existing chemicals based on the CSCL Japan*. Tokyo, Chemicals Inspection and Testing Institute.

Clay PF, Spittler TM (1983) Determination of airborne volatile nitrogen compounds using four independent techniques. In: *National Conference on Management of Uncontrolled Hazardous Waste Sites*, 31 October – 2 November 1983, Washington, DC. Silver Spring, MD, Hazardous Materials Control Research Institute/Consultants, pp. 100–104.

Clayton JW, Barnes JR, Hood DB, Schepers GWH (1963) The inhalation toxicity of dimethylformamide. *American Industrial Hygiene Association journal*, 24:144–154.

Conor Pacific Environmental (1998) *A report on multimedia exposures to selected PSL2 substances*. Prepared by Conor Pacific Environmental (formerly Bovar Environmental) and Maxxam Analytics Inc. for Health Canada, Ottawa, Ontario (Project No. 741-6705; Contract No. DSS File No. 025SS.H4078-6-C574).

Cragin DW, Lewis SC, McKee RH (1990) A dominant lethal test of dimethyl formamide. *Environmental and molecular mutagenesis*, 15(Suppl.17):14 (Abstract 44).

Craig DK, Weir RJ, Wagner W, Groth D (1984) Subchronic inhalation toxicity of dimethylformamide in rats and mice. *Drug and chemical toxicology*, 7:551–571.

Crump K (1995) Calculation of benchmark doses from continuous data. *Risk analysis*, 15(1):79–89.

Crump KS, Van Landingham C (1996) *BENCH_C: A Fortran program to calculate benchmark doses from continuous data*. Ruston, LA, ICF Consulting.

Curtis C, Lima A, Lozano SJ, Veith GD (1982) Evaluation of a bacterial bioluminescence bioassay as a method for predicting acute toxicity of organic chemicals to fish. In: Pearson JG, Foster RB, Bishop WE, eds. *Aquatic toxicity and hazard assessment: Fifth conference*. Philadelphia, PA, American Society for Testing and Materials, pp. 170–178 (ASTM Special Technical Publication 766).

Davis CS (1997) *Air dispersion modelling of phenol, final report*. Prepared by Bovar Environmental for the Chemicals Evaluation Division, Environment Canada, September (BE Project 74171-13).

DMER, AEL (1996) Pathways analysis using fugacity modelling of *N,N*-dimethylformamide for the second Priority Substances List. Prepared for Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, by Don Mackay Environmental Research, Peterborough, Ontario, and Angus Environmental Limited, Don Mills, Ontario.

Dojlido JR (1979) Investigations of biodegradability and toxicity of organic compounds. Washington, DC, US Environmental Protection Agency (EPA-600/2-79-163) [cited in Howard, 1993].

Drouet D'Aubigny F, Roquelaure Y, Bertrand L, Caillon M, Calès P (1998) [Hepatitis attributable to dimethylformamide with re-exposure.] *Gastroenterologie clinique et biologique*, 22:745–746 (in French).

Druckrey H, Preussmann R, Ivankovic S, Schmähel D (1967) [Organotropic carcinogenic effects of 65 different *N*-nitroso-compounds on BD rats.] *Zeitschrift für Krebsforschung*, 69:103–201 (in German).

Ducatman AM, Conwill DE, Crawl J (1986) Germ cell tumors of the testicle among aircraft repairmen. *Journal of urology*, 136:834–836.

Eben A, Kimmerle G (1976) Metabolism studies of *N,N*-dimethylformamide. III. Studies about the influence of ethanol in persons and laboratory animals. *International archives of occupational and environmental health*, 36:243–265.

Eberling CL (1980) Dimethylformamide. In: Kirk RE, Othmer DF, Grayson M, Eckroth DV, eds. *Kirk-Othmer encyclopedia of chemical technology*, 3rd ed. Vol. 11. New York, NY, John Wiley & Sons, pp. 263–268.

El Jay A (1996) Toxic effects of organic solvents on the growth of *Chlorella vulgaris* and *Selenastrum capricornutum* *Bulletin of environmental contamination and toxicology*, 57:191–198.

Elovaara E, Marselos M, Vainio H (1983) *N,N*-Dimethylformamide-induced effects on hepatic and renal xenobiotic enzymes with emphasis on aldehyde metabolism in the rat. *Acta Pharmacologica et Toxicologica*, 53:159–165.

Environment Agency Japan (1985) *Chemicals in the environment — Report on environmental survey and wildlife monitoring of chemicals in F.Y. 1982 and 1983*. Tokyo, Environment Agency Japan, Department of Environmental Health, Office of Health Studies, March, p. 50.

Environment Agency Japan (1996) *Chemicals in the environment — Report on environmental survey and wildlife monitoring of chemicals in F.Y. 1994*. Tokyo, Environment Agency Japan, Environmental Health and Safety Division, May, p. 119.

Environment Canada (1998) *PSL2 technical report for N,N-dimethylformamide (1995–1996 data)*. Prepared by H. Atkinson, Use Patterns Section, Chemicals Control Division, Commercial Chemicals Evaluation Branch, Environment Canada (unpublished and protected).

Environment Canada (1999a) *Supporting document for the environmental assessment of dimethylformamide, CEPA Priority Substances List*. Hull, Quebec, Environment Canada, Commercial Chemicals Evaluation Branch (unpublished).

Concise International Chemical Assessment Document 31

- Environment Canada (1999b) *PSL2 additional information on use pattern of DMF obtained from industry in 1999*. Prepared by C. Whittall, Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada (unpublished and protected).
- European Chemicals Bureau (1996a) *Trimethylamine*. IUCLID (International Uniform Chemical Information Database).
- European Chemicals Bureau (1996b) *Dimethylamine*. IUCLID (International Uniform Chemical Information Database).
- Evans EL, Mitchell AD (1981) Effects of 20 coded chemicals on sister chromatid exchange frequencies in cultured Chinese hamster cells. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 538–550 (Progress in Mutation Research, Vol. 1).
- Ewing BB, Chian ESK, Cook JC, DeWalle FB, Evans CA, Hopke PK, Kim JH, Means JC, Milberg R, Perkins EG, Sherwood JD, Wadlin WH (1977) *Monitoring to detect previously unrecognized pollutants in surface waters*. Washington, DC, US Environmental Protection Agency (EPA 560/6-77-015A).
- Fail PA, George JD, Grizzle RB, Heindel JJ (1998) Formamide and dimethylformamide: reproductive assessment by continuous breeding in mice. *Reproductive toxicology*, 12:317–332.
- Falck K, Partanen P, Sorsa M, Suovaniemi O, Vainio H (1985) Mutascreen, an automated bacterial mutagenicity assay. *Mutation research*, 150:119–125.
- Farhi M, Morel M, Cavigneaux A (1968) Dimethylformamide $\text{HCON}(\text{CH}_3)_2$. *Cahier de notes documentaires*, 50:91–93.
- Fersht AR, Requena Y (1971) Free energies of hydrolysis of amides and peptides in aqueous solution at 25 degrees Celsius. *Journal of the American Chemical Society*, 93:3499–3504.
- Figge K, Dommrose AM, Rabel W, Zerhau W (1987) Sammel- und analysensystem zur bestimmung organischer spurenstoffe in der atmosphäre. *Fresenius' Zeitschrift für Analytische Chemie*, 327:279–292 [cited in BUA, 1994].
- Finlayson-Pitts BJ, Pitts JN Jr (1986) *Atmospheric chemistry: fundamentals and experimental techniques*. New York, NY, John Wiley & Sons.
- Fiorito A, Larese F, Molinari S, Zanin T (1997) Liver function alterations in synthetic leather workers exposed to dimethylformamide. *American journal of industrial medicine*, 32:255–260.
- Forsyth A (1985) *Mammals of the Canadian wild*. Camden East, Ontario, Camden House Publishing Ltd.
- Frost AA, Pearson RG (1962) *Kinetics and mechanism*. New York, NY, John Wiley and Sons Inc.
- Frumin E, Brathwaite M, Towne W, Levin SM, Baker DB, Monaghan SV, Landrigan PJ, Marshal EG, Melius JM (1989) Testicular cancer in leather workers — Fulton County, New York. *Morbidity and mortality weekly report*, 38:105–114.
- Fujishiro K, Imazu K, Makita Y, Inoue N (1996) Alterations of hepatic drug metabolising system due to dimethylformamide (DMF). *Fukuoka Igaku Zasshi*, 87(7):162–168.
- Garner RC, Welch A, Pickering C (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 280–284 (Progress in Mutation Research, Vol. 1).
- Gatehouse D (1981) Mutagenic activity of 42 coded compounds in the "microtiter" fluctuation test. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 376–386 (Progress in Mutation Research, Vol. 1).
- Gescher A (1990) *N,N*-Dimethylformamide. In: Buhler DR, Reed DJ, eds. *Ethel Browning's toxicity and metabolism of industrial solvents. Vol. 2*. New York, NY, Elsevier, pp. 149–159.
- Gescher A (1993) Metabolism of *N,N*-dimethylformamide: key to the understanding of its toxicity. *Chemical research in toxicology*, 6:245–251.
- Government of Canada (in press) *Canadian Environmental Protection Act. Priority Substances List Assessment Report. N,N*-Dimethylformamide. Ottawa, Ontario, Environment Canada and Health Canada.
- Grasselli JG, ed. (1973) *Atlas of spectral data and physical constants for organic compounds*. Cleveland, OH, Chemical Rubber Publishing Co., 539 pp.
- Green NR, Savage JR (1978) Screening of safrole, eugenol, their ninhydrin positive metabolites and selected secondary amines for potential mutagenicity. *Mutation research*, 57(2):115–121.
- Groth G, Kronauer K, Freundt KJ (1994) Effects of *N,N*-dimethylformamide and its degradation products in zebrafish embryos. *Toxicology in vitro*, 8:401–406.
- Gubser H (1969) Probleme bei der Reinigung von Chemieabwässern. *Gas-Wasser-Abwasser*, 49:175–181.
- Guirguis S (1981) Dimethylformamide intoxication in acrylic fiber production. *Giornale Italiano di Medicina del Lavoro*, 3:137–140.
- Haber I, Heberer H, Schneider G, Leuschke W (1990) [Zytogenetic examinations of exposed workers in an acrylic fibres synthesizing plant.] *Wissenschaft und Umwelt*, 4:183–190 (in German).
- Hala E, Wichterle I, Polak J, Boublik T (1968) *Vapour liquid equilibrium data at normal pressures*. Oxford, Pergamon Press, 541 pp. [cited in DMER & AEL, 1996].
- Hamm A (1972) Schlammbehandlung und schlammabbauleistung beim abbau industrielle abwasserstoffe in labor-belebtschlammanlagen. *Müncher Beiträge zur Abwasser-, Fischerei- und Flussbiologie*, 22:79–91.
- Hanasono GK, Fuller RW, Broddle WD, Gibson WR (1977) Studies on the effects of *N,N*-dimethylformamide on ethanol disposition and on monoamine oxidase activity in rats. *Toxicology and applied pharmacology*, 39:461–472 [cited in WHO, 1991].
- Hansch C, Leo A, Hoekman D (1995) *Exploring QSAR. Hydrophobic, electronic, and steric constants*. Washington, DC, American Chemical Society, p. 6 (ACS Professional Reference Book).
- Hansen E, Meyer O (1990) Embryotoxicity and teratogenicity study in rats dosed epicutaneously with dimethylformamide (DMF). *Journal of applied toxicology*, 10:333–338.
- Haskell Laboratory (1960) *Ninety-day feeding study with dimethylformamide and dimethylacetamide*. Washington, DC, US

N,N-Dimethylformamide

Environmental Protection Agency (TSCA submission; Document Identification No. 869600002325; Microfiche No. NTIS/OTS0572893).

Hayon E, Iyata T, Lichtin NN, Simic M (1970) Sites of attack of hydroxyl radicals on amides in aqueous solution. *Journal of the American Chemical Society*, 92:3898–3903.

Health Canada (1994) *Human health risk assessment for Priority Substances*. Ottawa, Ontario, Minister of Supply and Services, 36 pp. (ISBN 0-662-22126-5).

Hellwig J, Merkle J, Klimisch HJ, Jäckh R (1991) Studies on the prenatal toxicity of *N,N*-dimethylformamide in mice, rats and rabbits. *Food and chemical toxicology*, 29:193–201.

Herrold KM (1969) Aflatoxin induced lesions in Syrian hamsters. *British journal of cancer*, 23:655–660.

Howard PH, ed. (1993) *Handbook of environmental fate and exposure data for organic chemicals*. Vol. 4. *Solvents 2*. Boca Raton, FL, Lewis Publishers.

Howe RB (1995) *THRESH: A computer program to compute a reference dose from quantal animal toxicity data using the benchmark dose method*. Ruston, LA, ICF Kaiser Engineers, Inc.

Huang J, Kuo H, Ho C, Chen T, Chang W (1998) Dimethylformamide-induced occupational liver injury — a case report. *Kaohsiung journal of medical science*, 14:655–658.

Hubbard SA, Green MHL, Bridges BA, Wain AJ, Bridges JW (1981) Fluctuation test with S9 and hepatocyte activation. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 361–370 (Progress in Mutation Research, Vol. 1).

Hughes JS, Vilkas AG (1983) Toxicity of *N,N*-dimethylformamide used as a solvent in toxicity tests with the green alga *Selenastrum capricornutum* *Bulletin of environmental contamination and toxicology*, 31:98–104.

Hundley SG, Lieder PH, Valentine R, Malley LA, Kennedy GL Jr (1993a) Dimethylformamide pharmacokinetics following inhalation exposures to rats and mice. *Drug and chemical toxicology*, 16:21–52.

Hundley SG, McCooley KT, Lieder PH, Hurtt ME, Kennedy GL Jr (1993b) Dimethylformamide pharmacokinetics following inhalation exposures in monkeys. *Drug and chemical toxicology*, 16:53–79.

Hurtt ME, McCooley KT, Placke ME, Kennedy GL (1991) Ten-day repeated-exposure inhalation study of dimethylformamide (DMF) in cynomolgus monkeys. *Toxicology letters*, 59:229–237.

Hurtt ME, Placke ME, Killinger JM, Singer AW, Kennedy GL Jr (1992) 13-week inhalation toxicity study of dimethylformamide (DMF) in cynomolgus monkeys. *Fundamental and applied toxicology*, 18:596–601.

IARC (1989) Dimethylformamide. In: *Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting*. Lyon, International Agency for Research on Cancer, pp. 171–197; 446–447 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 47).

IARC (1999) Dimethylformamide. In: *Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide*. Lyon, International Agency for Research on Cancer, pp. 545–574

(IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 71, Part Two).

Ichinotsubo D, Mower H, Mandel M (1981) Mutagen testing of a series of paired compounds with the Ames *Salmonella* testing system. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 298–301 (Progress in Mutation Research, Vol. 1).

Ikeda M (1996) *N,N*-Dimethylformamide. In: *Biological monitoring of chemical exposure in the workplace*. Vol. 1. Geneva, World Health Organization, pp.168–174.

Imazu K, Fujishiro K, Inoue N (1992) Effects of dimethylformamide on hepatic microsomal monooxygenase system and glutathione metabolism in rats. *Toxicology*, 72:41–50.

Imazu K, Fujishiro K, Inoue N (1994) Liver injury and alterations of hepatic microsomal monooxygenase system due to dimethylformamide (DMF) in rats. *Fukuoka Acta Medica*, 85(5):147–153.

IPCS (1994) *Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 170).

IPCS (1999) *International Chemical Safety Card — N,N-Dimethylformamide*. Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0457).

Ito N (1982) Unscheduled DNA synthesis induced by chemical carcinogens in primary cultures of adult rat hepatocytes. *Mie medical journal*, 32(1):53–60.

Janicki RH, Kinter WB (1971) DDT inhibits Na⁺, K⁺, Mg²⁺-ATPase in the intestinal mucosa and gills of marine teleosts. *Nature: New Biology*, 233.

Johnson WW, Finley MT (1980) *Handbook of acute toxicity of chemicals to fish and aquatic invertebrates*. Washington, DC, US Department of the Interior, Fish and Wildlife Service, 83 pp. (Resource Publication 137).

Jotz MM, Mitchell AD (1981) Effects of 20 coded chemicals on the forward mutation frequency at the thymidine kinase locus in L5178Y mouse lymphoma cells. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 580–593 (Progress in Mutation Research, Vol. 1).

Kang-De C, Hui-Lan Z (1981) Observation on the effects of dimethylformamide on human health. In: *Abstracts of the 9th International Congress on Occupational Health in the Chemical Industry*, 15–17 September 1981, Aswan, Egypt, pp. 22–23 [cited in WHO, 1991].

Kawai T, Yasugi T, Mizunuma K, Watanabe T, Cai S, Huang M, Xi L, Qu J, Yao B, Ikeda M (1992) Occupational dimethylformamide exposure. 2. Monomethylformamide excretion in urine after occupational dimethylformamide exposure. *International archives of occupational and environmental health*, 63(7):455–460.

Kawasaki M (1980) Experiences with the test scheme under the chemical control law of Japan: an approach to structure–activity correlations. *Ecotoxicology and environmental safety*, 4:444–454.

Kelly TJ, Ramamurthi M, Pollack AJ, Spicer CW, Culpitt LT (1993) *Ambient concentration summaries for Clean Air Act Title III*

Concise International Chemical Assessment Document 31

- Hazardous Air Pollutants*. Washington, DC, US Environmental Protection Agency (EPA Contract No. 68-D80082).
- Kelly TJ, Mukund R, Spicer CW, Pollack AJ (1994) Concentrations and transformations of hazardous air pollutants. What we know and don't know about the CAAA's 189 hazardous air pollutants. *Environmental science and technology*, 28(8):378A–387A.
- Kennedy GL Jr (1986) Biological effects of acetamide, formamide, and their monomethyl and dimethyl derivatives. *CRC critical reviews in toxicology*, 17:129–182.
- Kennedy GL Jr, Sherman H (1986) Acute and subchronic toxicity of dimethylformamide and dimethylacetamide following various routes of administration. *Drug and chemical toxicology*, 9:147–170.
- Kimber I, Weisenberger C (1989) A murine local lymph node assay for the identification of contact allergens. Assay development and results of an initial validation study. *Archives of toxicology*, 63:274–282.
- Kimmerle G, Eben A (1975a) Metabolism studies of *N,N*-dimethylformamide. I. Studies in rats and dogs. *Internationaleles Archiv für Arbeitsmedizin*, 34:109–126.
- Kimmerle G, Eben A (1975b) Metabolism studies of *N,N*-dimethylformamide. II. Studies in persons. *Internationaleles Archiv für Arbeitsmedizin*, 34:127–136.
- Kirkhart B (1981) Micronucleus test on 21 compounds. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 698–704 (Progress in Mutation Research, Vol. 1).
- Klaunig JE, Goldblatt PJ, Hinton DE, Lipsky MM, Trump BF (1984) Carcinogen induced unscheduled DNA synthesis in mouse hepatocytes. *Toxicologic pathology*, 12(2):119–125.
- Klug S, Merker HJ, Jooackh R (1998) Potency of monomethyl-, dimethylformamide and some of their metabolites to induce abnormal development in a limb bud organ culture. *Toxicology in vitro*, 12(2):123–132.
- Kommineni C (1973) *Pathological studies of aflatoxin fractions and dimethylformamide in MRC rats*. Omaha, NB, University of Nebraska, December 1972 (Dissertation) [cited in WHO, 1991].
- Koudela K, Spazier K (1979) [Effect of dimethylformamide on human peripheral lymphocytes.] *Ceskoslovenska Hygiena*, 24:432–436 (in Czechoslovakian with English abstract).
- Koudela K, Spazier K (1981) [Results of cytogenetic examination of persons working in the environment of increased concentration of dimethylformamide vapours in the atmosphere.] *Pracovni Lékarství*, 33:121–123 (in Czechoslovakian) [cited in IARC, 1999].
- Krivanek ND, McLaughlin M, Fayerweather WE (1978) Monomethylformamide levels in human urine after repetitive exposure to dimethylformamide vapour. *Journal of occupational medicine*, 20:179–182.
- Langlois S, Broche A (1964) *Étude cinétique de l'hydrolyse des amides N,N-disubstitués I. Dimethylformamide*. Report presented to the Chemical Society, pp. 812–816 (No. 148).
- Lauwerys RR, Kivits A, Lhoir M, Rigolet P, Houbeau D, Buchet JP, Roels HA (1980) Biological surveillance of workers exposed to dimethylformamide and the influence of skin protection on its percutaneous absorption. *International archives of occupational and environmental health*, 45:189–203.
- Leblanc GA, Surprenant DC (1983) The acute and chronic toxicity of acetone, dimethyl formamide and triethylene glycol to *Daphnia magna* (Straus). *Archives of environmental contamination and toxicology*, 12:305–310.
- Levin SM, Baker DB, Landrigan PJ, Monaghan SV, Frumin E, Braithwaite M, Towne W (1987) Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet*, ii:1153.
- Lewis SC, Rinehart WE, Schroeder RE, Thackara JW (1979) Dominant lethal mutagenic bioassay of dimethyl formamide (DMF). *Environmental mutagenesis*, 1:166 (Abstract Ea-7).
- Lewis SC, Schroeder RE, Kennedy GL Jr (1992) Developmental toxicity of dimethylformamide in the rat following inhalation exposure. *Drug and chemical toxicology*, 15:1–14.
- Lipski K (1982) Liquid chromatographic determination of dimethylformamide, methylene bisphenyl isocyanate, and methylene bisphenyl amine in air samples. *Annals of occupational hygiene*, 25:1–4.
- Llewellyn GC, Hastings WS, Kimbrough TD (1974) The effects of dimethylformamide on female Mongolian gerbils, *Meriones unguiculatus*. *Bulletin of environmental contamination and toxicology*, 11:467–473.
- Lundberg I, Pehrsson A, Lundberg S, Kronevi T, Lidums V (1983) Delayed dimethylformamide biotransformation after high exposures in rats. *Toxicology letters*, 17:29–34.
- Lyle WH (1979) Alcohol interaction with a workplace chemical. *Occupational health*, 5:265–267.
- Lyle WH, Spence TWM, McKinney WM, Duckers K (1979) Dimethylformamide and alcohol intolerance. *British journal of industrial medicine*, 36:63–66.
- MacDonald DJ (1981) *Salmonella*/microsome tests on 42 coded chemicals. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 285–297 (Progress in Mutation Research, Vol. 1).
- Mackay D (1991) *Multimedia environmental models: The fugacity approach*. Chelsea, MI, Lewis Publishers, 257 pp.
- Mackay D, Paterson S (1991) Evaluating the multimedia fate of organic chemicals: A Level III fugacity model. *Environmental science and technology*, 25:427.
- Major J, Hudák A, Kiss G, Jakab MG, Szaniszló J, Náray N, Nagy I, Tompa A (1998) Follow-up biological and genotoxicological monitoring of acrylonitrile- and dimethylformamide-exposed viscose rayon plant workers. *Environmental and molecular mutagenesis*, 31:301–310.
- Malley LA, Slone TW Jr, Van Pelt C, Elliott GS, Ross PE, Stadler JC, Kennedy GL Jr (1994) Chronic toxicity/oncogenicity of dimethylformamide in rats and mice following inhalation exposure. *Fundamental and applied toxicology*, 23:268–279.
- Marsella JA (1994) Formic acid and derivatives. In: Kirk RE, Othmer DF, Kroschwitz JI, Howe-Grant M, eds. *Kirk-Othmer encyclopedia of chemical technology*, 4th ed. Vol. 11. New York, NY, Wiley, pp. 967–976.
- Martin CN, McDermid AC (1981) Testing of 42 coded compounds for their ability to induce unscheduled DNA repair synthesis in HeLa cells. In: DeSerres FJ, Ashby J, eds. *Evaluation*

N,N-Dimethylformamide

of short-term tests for carcinogens. Report of the International Collaborative Program. New York, NY, Elsevier, pp. 533–537 (Progress in Mutation Research, Vol. 1).

Martire G, Vricella G, Perfumo AM, DeLorenzo F (1981) Evaluation of the mutagenic activity of coded compounds in the *Salmonella* test. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 271–279 (Progress in Mutation Research, Vol. 1).

Massmann W (1956) Toxicological investigations on dimethylformamide. *British journal of industrial medicine*, 13:51–54.

Matsushima T, Takamoto Y, Shirai A, Sawamura M, Sugimura T (1981) Reverse mutation test on 42 coded compounds with the *E. coli* WP2 system. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 387–395 (Progress in Mutation Research, Vol. 1).

McGregor DF (1981) *Tier II mutagenic screening of 13 NIOSH priority compounds: N,N-Dimethylformamide* (Report No. 33; PB83-13390-0) [cited in Kennedy, 1986].

McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Caspary WJ (1988) Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay II: 18 coded chemicals. *Environmental and molecular mutagenesis*, 11:91–118.

McQueen CA, Kreiser DM, Williams GM (1983) The hepatocyte primary culture/DNA repair assay using mouse or hamster hepatocytes. *Environmental mutagenesis*, 5(1):1–8.

McQueen CA, Way BM, Williams GM (1988) Genotoxicity of carcinogens in human hepatocytes: application in hazard assessment. *Toxicology and applied pharmacology*, 96:360–366.

Mitchell AD, Rudd CJ, Caspary WJ (1988) Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: intralaboratory results for sixty-three coded chemicals tested at SRI International. *Environmental and molecular mutagenesis*, 12(Suppl. 13):37–101.

Mohn GR, Vogels-Bouter S, van der Horst-van der Zon J (1981) Studies on the mutagenic activity of 20 coded compounds in liquid tests using the multipurpose strain *Escherichia coli* K-12/343/113 and derivatives. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 396–413 (Progress in Mutation Research, Vol. 1).

Montelius J, Boman A, Wahlkvist H, Wahlberg JE (1996) The murine local lymph node assay: search for an alternative, more adequate, vehicle than acetone/olive oil (4:1). *Contact dermatitis*, 34:428–430.

Montelius J, Wahlkvist H, Boman A, Wahlberg JE (1998) Murine local lymph node assay for predictive testing of allergenicity: two irritants caused significant proliferation. *Acta Dermato-Venereologica*, 78:433–437.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E (1986) *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environmental mutagenesis*, 7:1–119.

Mráz J, Nohová H (1992a) Percutaneous absorption of *N,N*-dimethylformamide in humans. *International archives of occupational health*, 64:79–83.

Mráz J, Nohová H (1992b) Absorption, metabolism and elimination of *N,N*-dimethylformamide in humans. *International archives of occupational health*, 64:85–92.

Mráz J, Cross H, Gescher A, Threadgill MD, Flek J (1989) Differences between rodents and humans in the metabolic toxification of *N,N*-dimethylformamide. *Toxicology and applied pharmacology*, 98:507–516.

Mráz J, Jheeta P, Gescher A, Hyland R, Thummel K, Threadgill MD (1993) Investigation of the mechanistic basis of *N,N*-dimethylformamide toxicity. Metabolism of *N,N*-dimethylformamide and its deuterated isotopomers by cytochrome P450 2E1. *Chemical research in toxicology*, 6:197–207.

Muravieva SI (1983) [Improvement of the methods for monitoring the content of harmful substances in the air of worksite.] *Gigiena Truda i Professional'nye Zabolevaniya*, 6:39–41 (in Russian).

Muravieva SI, Anvaer LP (1979) [Determination of dimethylformamide and its metabolites in biological liquids by gas chromatographic method.] *Gigiena Truda i Professional'nye Zabolevaniya*, 6:58–59 (in Russian).

Myhr BC, Caspary WJ (1988) Evaluation of the L5178Y mouse lymphoma assay: intralaboratory results for sixty-three coded chemicals tested at Litton Bionetics, Inc. *Environmental and molecular mutagenesis*, 12(Suppl. 13):103–194.

Nagao M, Takahashi Y (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 302–331 (Progress in Mutation Research, Vol. 1).

Nakajima S (1970) Industrial products and pollution problems. *Nippon Kagaku Kogyo*, 18:2–3.

Nalecz-Jawecki G, Sawicki J (1999) Spirotox — a new tool for testing the toxicity of volatile compounds. *Chemosphere*, 38(14):3211–3218.

Natarajan AT, van Kesteren-van Leeuwen AC (1981) Mutagenic activity of 20 coded compounds in chromosome aberrations/sister chromatid exchanges assay using Chinese hamster ovary (CHO) cells. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 551–559 (Progress in Mutation Research, Vol. 1).

Nicolas F, Rodineau P, Rouzioux J-M, Tack I, Chabac S, Meram D (1990) Fulminant hepatic failure in poisoning due to ingestion of T61, a veterinary euthanasia drug. *Critical care medicine*, 18:573–575.

NIOSH (1977) *Manual of analytical methods. Vol. 3*. Cincinnati, OH, National Institute for Occupational Safety and Health (No. S-255).

NIOSH (1978) *Occupational health guideline for dimethylformamide*. Cincinnati, OH, National Institute for Occupational Safety and Health, 5 pp.

NIOSH (1983) *National occupational exposure survey (NOES), 1981–1983: estimated total male and female employees, actual observations and trade-named exposures to dimethyl formamide*. Cincinnati, OH, US Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Health Evaluations, and Field Studies, Surveillance Branch (unpublished database).

NIOSH (1994) *NIOSH manual of analytical methods*, 4th ed. Cincinnati, OH, National Institute for Occupational Safety and Health.

Concise International Chemical Assessment Document 31

- NTP (1992a) *NTP technical report on toxicity studies of N,N-dimethylformamide (CAS No. 68-12-2) administered by inhalation to F344/N rats and B6C3F₁ mice*. Research Triangle Park, NC, National Institutes of Health, National Toxicology Program, 44 pp. (Toxicity Report Series No. 22; NIH Publication No. 93-3345; NTIS Publication No. PB93-131936).
- NTP (1992b) *Final report on the reproductive toxicity of N,N-dimethylformamide (DMF) (CAS #68-12-2) in CD-1 Swiss mice*. Research Triangle Park, NC, National Institutes of Health, National Toxicology Program (NTIS Publication No. PB93-123842).
- Paika IJ, Beauchesne MT, Randall M, Schreck RR, Latt SA (1981) *In vivo* SCE analysis of 20 coded compounds. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 673–681 (Progress in Mutation Research, Vol. 1).
- Paoletti A, Iannaccone A (1982) [Toxicity hazard in a plant producing a synthetic leather.] *Annali dell'Istituto Superiore di Sanità*, 18:567–570 (in Italian).
- Paoletti A, Fabri G, Masci O (1982a) [Alcohol-intolerance due to solvents: comparison between dimethylformamide and trichloroethylene.] *Annali dell'Istituto Superiore di Sanità*, 18 (Suppl.):1099–1100 (in Italian).
- Paoletti A, Fabri G, Bettolo PM (1982b) [An unusual case of abdominal pain due to dimethylformamide intoxication.] *Minerva Medica*, 73:3407–3410 (in Italian).
- Pellizzari EO (1977) *The measurement of carcinogenic vapors in ambient atmosphere*. Research Triangle Park, NC, US Environmental Protection Agency, Office of Research and Development, Environmental Sciences Research Laboratory (Contract No. 68-02-1228).
- Perry DL, Chuang CC, Jungclaus GA, Warner JS (1979) *Identification of organic compounds in industrial effluent discharges*. Washington, DC, US Environmental Protection Agency (EPA 600/4-79-016).
- Perry PE, Thomson EJ (1981) Evaluation of the sister chromatid exchange method in mammalian cells as a screening system for carcinogens. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 560–569 (Progress in Mutation Research, Vol. 1).
- Peterson HG, Ruecker N, Dennison K, Moody M (1997) *Toxicity testing of the compound N,N-dimethylformamide to phytoplankton (green algae, diatoms, and cyanobacteria) and a vascular plant (duckweed) — Draft*. Saskatoon, Saskatchewan, Saskatchewan Research Council (R-1640-18-E-97).
- Pitts JN Jr, Grosjean D, Van Cauwenberghe K, Schmid JP, Fitz DR (1978) Photooxidation of aliphatic amines under simulated atmospheric conditions: formation of nitrosamines, nitramines, amides and photochemical oxidant. *Environmental science and technology*, 12:946–953.
- Poirier SH, Knuth ML, Anderson-Bouchou CD, Brooke LT, Lima AR, Shubat PJ (1986) Comparative toxicity of methanol and N,N-dimethylformamide to freshwater fish and invertebrates. *Bulletin of environmental contamination and toxicology*, 37:615–621.
- Portmann JE, Wilson KW (1971) *The toxicity of 140 substances to the brown shrimp and other marine animals*, 2nd ed. North Wales, Ministry of Agriculture, Fisheries and Food, 12 pp. (Shellfish Information Leaflet 22).
- Potter HP (1973) Dimethylformamide-induced abdominal pain and liver injury. *Archives of environmental health*, 27:340–341.
- Prinn R, Cunnold D, Rasmussen R, Simmonds P, Alyea F, Crawford A, Fraser P, Rosen R (1987) Atmospheric trends in methylchloroform and the global average for the hydroxyl radical. *Science*, 238:945–950.
- Purchase IFH, Longstaff E, Ashby J, Styles JA, Anderson D, Lefevre PA, Westwood RR (1978) An evaluation of 6 short-term tests for detecting organic chemical carcinogens. *British journal of cancer*, 37:873–903.
- Rajini PS, Krishnakumari MK, Majumder SK (1989) Cytotoxicity of certain organic solvents and organophosphorus insecticides to the ciliated protozoan *Paramecium caudatum* *Microbios*, 59:157–163.
- Redlich CA, Beckett SWS, Sparer J, Barwick KW, Riely CA, Miller H, Sigal SL, Shalat SL, Cullen MR (1988) Liver disease associated with occupational exposure to the solvent dimethylformamide. *Annals of internal medicine*, 108:680–686.
- Redlich CA, West AB, Fleming L, True LD, Cullen MR, Riely CA (1990) Clinical and pathological characteristics of hepatotoxicity associated with occupational exposure to dimethylformamide. *Gastroenterology*, 99:748–757.
- Riachi G, Michel P, François A, Ducrotte P, Laffineur G, Lerebours E, Colin R (1993) [Acute hepatic effects of exposure to dimethylformamide. Clinical and histological aspects.] *Gastroenterology and clinical biology*, 17:611–612 (in French).
- Richold M, Jones E (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 314–322 (Progress in Mutation Research, Vol. 1).
- Riddick JA, Bunger WB, Sakano TK (1986) *Techniques of chemistry*, 4th ed. Vol. II. *Organic solvents. Properties and methods of purification*. New York, NY, John Wiley & Sons, pp. 656; 1089–1091.
- Robinson DE, Mitchell AD (1981) Unscheduled DNA synthesis response of human fibroblasts, WI-38 cells, to 20 coded chemicals. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 517–527 (Progress in Mutation Research, Vol. 1).
- Romadina ES (1975) Direct action of microorganisms — one way of increasing the effectiveness of the biological purification of waste waters. In: Telitchenko MM, ed. *Biologicheskoe Samoochishchenie i Formirovanie Kachestva Vody Materialy Vsesoyuznogo Simpoziuma po Sanitarnoi*. Moscow, "Nauka," pp. 110–112.
- Rowland I, Severn B (1981) Mutagenicity of carcinogens and noncarcinogens in the *Salmonella*/microsome test. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 323–332 (Progress in Mutation Research, Vol. 1).
- Sabljić A (1984) Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. *Journal of agricultural and food chemistry*, 32:243–246.
- Saillenfait AM, Payan JP, Beydon D, Fabry JP, Langonne I, Sabate JP, Gallissot F (1997) Assessment of the developmental toxicity, metabolism, and placental transfer of N,N-dimethylformamide administered to pregnant rats. *Fundamental and applied toxicology*, 39:33–43.

N,N-Dimethylformamide

- Sakai T, Kageyama H, Araki T, Yosida T, Kuribayashi T, Masuyama Y (1995) Biological monitoring of workers exposed to *N,N*-dimethylformamide by determination of the urinary metabolites *N*-methylformamide and *N*-acetyl-S-(*N*-methylcarbamoyl) cysteine. *International archives of occupational and environmental health*, 67:125–129.
- Salamone MF, Heddle JA, Katz M (1981) Mutagenic activity of 41 compounds in the *in vivo* micronucleus assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 686–697 (Progress in Mutation Research, Vol. 1).
- Sanotsky IV, Muravieva SI, Zaeva GN, Anvaer L, Semiletkina NN (1978) [Metabolism of dimethylformamide depending on the intensity of its action.] *Gigiena Truda i Professional'nye Zabolevaniya*, 11:24–27 (in Russian).
- Sasaki S (1978) *The scientific aspects of the chemical substance control law in Japan. Aquatic pollutants: transformation and biological effects*. Oxford, Pergamon Press, 298 pp.
- Savolainen H (1981) Dose-dependent effects of peroral dimethylformamide administration on rat brain. *Acta Neuropathologica*, 53:249–252.
- Scott B (1998) *Fate of N,N-dimethylformamide in the environment. Review*. Burlington, Ontario, Environment Canada, National Water Research Institute, March.
- Sebaugh JL, Wilson JD, Tucker MW, Adams WJ (1991) A study of the shape of dose–response curves for acute lethality at low response: A “megadaphnia study.” *Risk analysis*, 11:633–640.
- Seiji K, Inoue O, Cai S-X, Kawai T, Watanabe T, Ikeda M (1992) Increase in sister chromatid exchange rates in association with occupational exposure to *N,N*-dimethylformamide. *International archives of occupational and environmental health*, 64:65–67 [cited in IARC, 1999].
- Sharkawi M (1979) Inhibition of alcohol dehydrogenase by dimethylformamide and dimethylsulfoxide. *Toxicology letters*, 4:493–497 [cited in WHO, 1991].
- Shelton DR, Tiedje JM (1981) *Development of tests for determining anaerobic biodegradation potential*. East Lansing, MI, Michigan State University, Department of Crop Soil Science (EPA 560/5-81-013; NTIS Publication No. PB84-166495).
- Sheveleva GA, Sivochalova OV, Osina SA, Salnikova LS (1977) Permeability of the placenta to dimethylformamide. *Akusherstvo i ginekologiya (Moscow)*, 5:44–45 [cited in Saillenfait et al., 1997].
- Sheveleva GA, Strekalova EE, Chirkova EM (1979) A study of the embryotropic, mutagenous and gonadotropic effect of dimethylformamide with exposure by inhalation. In: *The toxicology of new industrial chemicals. Vol. 15*. Moscow, Medizina, pp. 1–4.
- Shumilina AV (1991) Experimental study of transplacental passage of dimethylformamide and toluene. *Akusherstvo i ginekologiya (Moscow)*, 11:49–51 [cited in Saillenfait et al., 1997].
- Sickles JE, Wright RS, Sutcliffe CR, Blackard AL, Dayton DP (1980) *Smog chamber studies of the reactivity of volatile organic compounds*. Presented at the 73rd Annual Meeting of the Air Pollution Control Association, Montreal, Quebec. Research Triangle Park, NC, Research Triangle Institute (80-50.1).
- Simmon VF, Shepherd GF (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 333–342 (Progress in Mutation Research, Vol. 1).
- Skopek TR, Andon BM, Kaden DA, Thilly WG (1981) Mutagenic activity of 42 coded compounds using 8-azaguanine resistance as a genetic marker in *Salmonella typhimurium*. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 371–375 (Progress in Mutation Research, Vol. 1).
- Sram RJ, Landa K, Hola N, Roznickova I (1985) The use of the cytogenetic analysis of peripheral lymphocytes as a method for checking the level of MAC in Czechoslovakia. *Mutation research*, 147:322 (Abstract 87) [cited in IARC, 1999].
- SRI International (1994) CEH data summary: Dimethylformamide — North America. In: *Chemical economics handbook (CEH)*. Menlo Park, CA, SRI International, pp. 641.3000 A-G.
- Stransky V (1986) The determination of *N,N*-dimethylformamide in working atmosphere by the method of gas chromatography after sampling on activated charcoal. *Pracovni Lekarstvi*, 38:15–19.
- Stratton GW (1985) The influence of solvent type on solvent–pesticide interactions in bioassays. *Archives of environmental contamination and toxicology*, 14:651–658.
- Stratton GW (1987) Toxic effects of organic solvents on the growth of blue-green algae. *Bulletin of environmental contamination and toxicology*, 38:1012–1019.
- Stratton GW, Smith TM (1988) Interaction of organic solvents with the green alga *Chlorella pyrenoidosa*. *Bulletin of environmental contamination and toxicology*, 40:736–742.
- Syracuse Research Corporation (1988) *Support for chemical nomination and selection process of the National Toxicology Program, Executive summary of data, Dimethylformamide (68-12-2) — Draft*. Syracuse, NY, Syracuse Research Corporation, Chemical Hazard Assessment Division.
- Szabo LG (1972) Effect of formamide and dimethyl-formamide on germination. *Acta Agronomica Academiae Scientiarum Hungaricae*, 21:428–430.
- Taccola A, Catenacci G, Baruffini A (1981) Cardiotoxicity of dimethylformamide (DMF). Electrocardiographic findings and continuous electrocardiographic monitoring (Holter). *Giornale Italiano di Medicina del Lavoro*, 3:149–151.
- Thé JL (1998) *Carbon disulfide study*. Waterloo, Ontario, Lakes Environmental Consultants Inc.
- Thomson JA (1981) Mutagenic activity of 42 coded compounds in the lambda induction assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 224–235 (Progress in Mutation Research, Vol. 1).
- Thonke M, Dittmann W (1966) Dimethylformamide in biological treatment of sewage. *Fortschritte der Wasserchemie und Ihrer Grenzgebiete*, 4:277.
- Tolot F, Arcadio FI, Lenglet J-P, Roche L (1968) [Intoxication by dimethylformamide.] *Archives des Maladies Professionnelles de Médecine du Travail et de Sécurité Sociale*, 29:714–717 (in French).

Concise International Chemical Assessment Document 31

- Tomasini M, Todaro A, Piazzoni M, Peruzzo GF (1983) [Exposure to dimethylformamide: study of 14 cases.] *Medicina del Lavoro*, 74:217–220 (in Italian).
- Topham JC (1980) Do induced sperm-head abnormalities in mice specifically identify mammalian mutagens rather than carcinogens? *Mutation research*, 74:379–387.
- Topham JC (1981) Evaluation of some chemicals by the sperm morphology assay. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 718–720 (Progress in Mutation Research, Vol. 1).
- Trueman RW (1981) Activity of 42 coded compounds in the *Salmonella* reverse mutation test. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 343–350 (Progress in Mutation Research, Vol. 1).
- Tsushima T, Matter BE (1981) Activity of coded compounds in the micronucleus test. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 705–711 (Progress in Mutation Research, Vol. 1).
- Ursin C (1985) Degradation of organic chemicals at trace levels in seawater and marine sediment: the effect of concentration on the initial fractional turnover rate. *Chemosphere*, 14:1539–1550 [cited in Howard, 1993].
- US EPA (1986) *Health and environmental effects profile for N,N-dimethylformamide*. Cincinnati, OH, US Environmental Protection Agency, 115 pp. (EPA/600/X-86/141).
- US EPA (1997) *OPPT high production volume chemicals (1997)*. Washington, DC, US Environmental Protection Agency, Office of Pollution, Prevention and Toxics.
- US EPA (1999) *Wildlife exposure factors handbook. Vol. I*. Washington, DC, US Environmental Protection Agency, Office of Research and Development (<http://www.epa.gov/ncea/wefh.htm>).
- Venitt S, Crofton-Sleigh C (1981) Mutagenicity of 42 coded compounds in a bacterial assay using *Escherichia coli* and *Salmonella typhimurium*. In: DeSerres FJ, Ashby J, eds. *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program*. New York, NY, Elsevier, pp. 351–360 (Progress in Mutation Research, Vol. 1).
- Walrath J, Fayerweather WE, Gilby PG, Pell S (1989) A case–control study of cancer among Du Pont employees with potential for exposure to dimethylformamide. *Journal of occupational medicine*, 31:432–438.
- Walrath J, Fayerweather WE, Gilby P (1990) [Case–control study of the incidence of cancers in employees of the Du Pont de Nemours company who have potentially been exposed to dimethylformamide.] *Cahiers de notes documentaires*, 140:708–712 (in French).
- Wang JD, Lai MY, Chen JS, Lin JM, Chiang JR, Shiau SJ, Chang WS (1989) Dimethylformamide induced liver and muscle damage among synthetic leather workers: are hepatitis B carriers more susceptible? In: *Fifth International Congress of Toxicology*, Brighton, 16–21 July 1989, p. 143 (Abstract 428).
- Wang J-D, Lai M-Y, Chen J-S, Lin J-M, Chiang J-R, Shiau S-J, Chang W-S (1991) Dimethylformamide-induced liver damage among synthetic leather workers. *Archives of environmental health*, 46:161–166.
- Weiss G (1971) [Industrial dimethylformamide intoxication and the question of its recognition as an occupational disease.] *Zentralblatt für Arbeitsmedizin*, 11:345–346 (in German).
- WHO (1991) *Dimethylformamide*. Geneva, World Health Organization, International Programme on Chemical Safety, 124 pp. (Environmental Health Criteria 114).
- Williams GM (1977) Detection of chemical carcinogens by unscheduled DNA synthesis in rat liver primary cell cultures. *Cancer research*, 37:1845–1851.
- Wilson HK, Ottley TW (1981) The use of a transportable mass spectrometer for the direct measurement of industrial solvents in breath. *Biomedical mass spectrometry*, 8:606–610.
- Wrbitzky R (1999) Liver function in workers exposed to *N,N*-dimethylformamide during the production of synthetic textiles. *International archives of occupational and environmental health*, 72(1):19–25.
- Wrbitzky R, Angerer J (1998) *N,N*-dimethylformamide — influence of working conditions and skin penetration on the internal exposure of workers in synthetic textile production. *International archives of occupational and environmental health*, 71(5):309–316.
- Yang C, Ger J, Lin S, Yang G, Deng J (1994) Abdominal colic occurred in workers in a dye manufacturing plant. *Veterinary and human toxicology*, 36:345 (Abstract 28).
- Ye G (1987) [The effect of dimethylformamide on the frequency of micronuclei in bone marrow polychromatic erythrocytes of mice.] *Zoological research*, 8:27–32 (in Chinese) [online abstract from *Biosis previews*].
- Yonemoto J, Suzuki S (1980) Relation of exposure to dimethylformamide vapor and the metabolite, methylformamide, in urine of workers. *International archives of occupational and environmental health*, 46:159–165.
- Ziegenfuss PS, Renaudette WJ, Adams WJ (1986) Methodology for assessing the acute toxicity of chemicals sorbed to sediments: testing the equilibrium partitioning theory. In: Poston TM, Purdy R, eds. *Aquatic toxicology and environmental fate*. Philadelphia, PA, American Society for Testing and Materials, pp. 479–493 (ASTM Special Technical Publication 921).

APPENDIX 1 — SOURCE DOCUMENT

Government of Canada (in press)

Copies of the *Canadian Environmental Protection Act Priority Substances List Assessment Report* (Government of Canada, in press) and unpublished supporting documentation for *N,N*-dimethylformamide may be obtained from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
Canada K1A 0H3

or

Environmental Health Centre
Health Canada
Address Locator: 0801A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0L2

Initial drafts of the supporting documentation and Assessment Report for DMF were prepared by staff of Health Canada and Environment Canada.

The environmental sections were reviewed externally by:

D. Andrews, Golder Associates Ltd.
K. Bolton, University of Toronto
N. Bunce, University of Guelph
R. Gensemer, Boston University
D. Hastie, York University
S. Mabury, University of Toronto
M. Mumtaz, Chinook Group Ltd.
C. Nalewajko, University of Toronto
M. Sheppard, EcoMatters Inc.

Sections of the supporting documentation pertaining to human health were reviewed externally by G. Kennedy, DuPont Haskell Laboratory for Toxicology and Industrial Medicine, to address adequacy of coverage.

Accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard identification and dose-response analyses were considered at a panel of the following members, convened by Toxicology Excellence in Risk Assessment on 14 February 2000 in Ottawa, Canada:

M.S. Abdel-Rahman, University of Medicine & Dentistry of New Jersey
C. Abernathy, US Environmental Protection Agency
J.P. Christopher, California Environmental Protection Agency
J.C. Collins, Solutia, Inc.
J.T. Colman, Syracuse Research Corporation
M. Mumtaz, Agency for Toxic Substances and Disease Registry
K.A. Poirier, Toxicology Excellence in Risk Assessment
J.E. Whalen, US Environmental Protection Agency

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on *N,N*-dimethylformamide was sent for review to institutions and organizations identified by IPCS after contact with IPCS National Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, International Programme on Chemical Safety, World Health Organization, Switzerland

M. Baril, Institut de Recherche en Santé et en Sécurité du Travail du Québec (IRSST), Canada

R. Benson, Drinking Water Program, US Environmental Protection Agency, USA

R.S. Chhabra, National Institute for Environmental and Health Sciences/National Institutes of Health (NIEHS/NIH), USA

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV), Germany

C. Hiremath, US Environmental Protection Agency, USA

H. Kafferlein, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nuremberg, Germany

F. Larese, Institute of Occupational Medicine, University of Trieste, Italy

H. Lendle, Product Safety, BASF AG, Germany

I. Mangelsdorf, Fraunhofer Institute for Toxicology and Aerosol Research, Germany

J. Mraz, Centre of Industrial Hygiene and Occupational Diseases, National Institute of Public Health, Czech Republic

P. Ridgeway, Health and Safety Executive, United Kingdom

P. Schulte, National Institute for Occupational Safety and Health, USA

E. Soderlund, Department of Environmental Medicine, National Institute of Public Health, Norway

D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia

P. Yao, Chinese Academy of Preventive Medicine, People's Republic of China

K. Ziegler-Skylakakis, Beratergremium für Umweltrelevante Altstoffe (BUA), Germany

Concise International Chemical Assessment Document 31

**APPENDIX 3 — CICAD FINAL REVIEW
BOARD****Helsinki, Finland, 26–29 June 2000****Members**

Mr H. Ahlers, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr T. Berzins, National Chemicals Inspectorate (KEMI), Solna, Sweden

Dr R.M. Bruce, Office of Research and Development, National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

Mr R. Cary, Health and Safety Executive, Liverpool, United Kingdom (*Rapporteur*)

Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Dr H. Choudhury, National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

Dr S. Dobson, Centre for Ecology and Hydrology, Monks Wood, Abbots Ripton, United Kingdom (*Chairman*)

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Ms K. Hughes, Priority Substances Section, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr G. Koennecker, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M. Meek, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr A. Nishikawa, Division of Pathology, Biological Safety Research Centre, National Institute of Health Sciences, Tokyo, Japan

Dr V. Riihimäki, Finnish Institute of Occupational Health, Helsinki, Finland

Dr J. Risher, Agency for Toxic Substances and Disease Registry, Division of Toxicology, US Department of Health and Human Services, Atlanta, GA, USA

Professor K. Savolainen, Finnish Institute of Occupational Health, Helsinki, Finland (*Vice-Chairman*)

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr S. Soliman, Department of Pesticide Chemistry, Faculty of Agriculture, Alexandria University, Alexandria, Egypt

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, NSW, Australia

Observer

Dr R.J. Lewis (representative of European Centre for Ecotoxicology and Toxicology of Chemicals), Epidemiology and Health Surveillance, ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, USA

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland (*Secretary*)

Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Younes, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

APPENDIX 4 — BENCHMARK DOSE CALCULATIONS

In subchronic inhalation assays in F344 rats, there was an increase in relative liver weight in females and increased cholesterol in both sexes at 50 ppm (150 mg/m³), with no clear dose-response (LOEC) (NTP, 1992a), progressive histopathological hepatic changes in both sexes at 400 and 800 ppm (1200 and 2400 mg/m³) (Craig et al., 1984), and hepatocellular necrosis in both sexes at 400 ppm (1200 mg/m³) (NTP, 1992a). B6C3F1 mice had hepatocellular hypertrophy at 50 ppm (150 mg/m³) (LOEC), in addition to significantly increased relative liver weight in both sexes without clear dose-response (NTP, 1992a) and hepatic cytomegaly at 150 ppm (450 mg/m³) and higher (Craig et al., 1984). No signs of toxicity were observed in monkeys exposed to up to 500 ppm (1500 mg/m³) (Hurt et al., 1992).

In a chronic inhalation bioassay in Crl:CD BR rats, at 100 ppm (300 mg/m³), there were significant increases in centrilobular hepatocellular hypertrophy (both sexes), hepatic accumulation of lipofuscin/haemosiderin (both sexes), and hepatic single-cell necrosis (females only). In mice [Crl:CD 1 (ICR)BR], at 25 ppm (75 mg/m³), there was centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females), and hepatic Kupffer cell hyperplasia/pigment accumulation (males) (Malley et al., 1994).

Data on dose-response following ingestion are limited to medium-term exposure studies. At 250 mg/kg body weight per day, liver cell enlargement was reported in Crl:CD rats; at 50 mg/kg body weight per day, relative liver weight was significantly increased in males (Kennedy & Sherman, 1986). In Wistar rats, relative liver weight was significantly increased at 69 mg/kg body weight per day, but no histopathological lesions were observed at doses up to 235 mg/kg body weight per day (Becci et al., 1983). In CD-1 mice, only mild histopathological changes were observed in the liver at 246 mg/kg body weight per day; at 96 mg/kg body weight per day, relative liver weight was significantly increased in females. No adverse effects were observed in beagle dogs administered up to 34.8 mg/kg body weight day in the diet for 13 weeks.

It should be noted that the lowest concentration (50 ppm [150 mg/m³]) at which effects were observed in the liver of rats (NTP, 1992a) in an inhalation assay is equivalent to an intake of 46.5 mg/kg body weight per day in rats,¹ which is consistent with the effects levels in Crl:CD rats (Kennedy & Sherman, 1986) and Wistar rats (Becci et al., 1983) following dietary exposure. The lowest concentration (50 ppm [150 mg/m³]) to which mice were exposed in the NTP (1992a) is equivalent to an intake of 200 mg/kg body weight per day,² which is consistent with the effect levels in the dietary assay in mice reported by Becci et al. (1983).

Reported incidence, benchmark concentrations (BMCs) at the 5% level, and associated *P*-values and goodness of fit statistics for effects on the liver for relevant end-points in the most robust medium- and long-term exposure studies for ingestion and inhalation, respectively, are presented in Tables 2 and 3.

For the discrete end-points, the BMC₀₅ is defined as the concentration of chemical that causes a 5% increase in incidence over the background response rate. It is calculated by first fitting the following model to the dose-response data (Howe, 1995):

$$P(d) = q_0 + (1 - q_0) [1 - e^{-q_1 d - q_2 d^2 - \dots - q_k d^k}]$$

where *d* is dose, *k* is the number of dose groups in the study, *P*(*d*) is the probability of the animal developing the effect at dose *d*, and *q_i* > 0, *i* = 1, ..., *k* is a parameter to be estimated.

The models were fit to the incidence data using THRESH (Howe, 1995), and the BMC₀₅s were calculated as the concentration *C* that satisfies

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to *k* minus the number of *q_i*'s whose estimates are non-zero. A *P*-value less than 0.05 indicates a significant lack of fit.

For the continuous end-points, the BMC₀₅ is defined as the dose that causes a 5% increase in the absolute risk of seeing an "adverse" response. This method utilizes the "hybrid" method of Crump (1995), in which the adverse response level in the control group is specified as 5%. That is, 5% of the animals in the control group would, by natural variation, have a response that would be considered adverse. Then, the probability of being adverse, as opposed to the response itself, is modelled.

The Weibull model was fit to each of the end-points using BENCH_C (Crump & Van Landingham, 1996):

$$P(d) = p_0 + (1 - p_0) [1 - e^{-(d/d_0)^k}]$$

where *d* is dose, *P*(*d*) is the probability of an adverse response at dose *d*, and *k*, *d₀*, and *p₀* are parameters to be estimated. The BMC₀₅ was then calculated as the concentration *C* such that

$$P(C) - P(0) = 0.05$$

An F-test was used to assess lack of fit of the model. A *P*-value less than 0.05 indicates lack of fit.

¹ 1 mg/m³ = 0.31 mg/kg body weight per day in rats (Health Canada, 1994).

² 1 mg/m³ = 1.33 mg/kg body weight per day in mice (Health Canada, 1994).

N,N-DIMETHYLFORMAMIDE**0457**

October 2000

CAS No: 68-12-2
RTECS No: LQ2100000
UN No: 2265
EC No: 616-001-00-X

Dimethylformamide
DMF
DMFA
N-formyldimethylamine
 C_3H_7NO / $HCON(CH_3)_2$
Molecular mass: 73.09

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Flammable. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames, NO sparks, and NO smoking. NO contact with oxidizing agents.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Above 58°C explosive vapour/air mixtures may be formed.	Above 58°C use a closed system, ventilation.	In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE		PREVENT GENERATION OF MISTS! AVOID EXPOSURE OF (PREGNANT) WOMEN!	
Inhalation	Abdominal pain. Diarrhoea. Nausea. Vomiting. Facial flushing.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED!	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap. Refer for medical attention.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Ventilation. Remove all ignition sources. Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. (Extra personal protection: complete protective clothing including self-contained breathing apparatus).	T Symbol R: 61-20/21-36 S: 53-45 Note: E UN Hazard Class: 3 UN Pack Group: III

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-30G35 NFPA Code: H1; F2; R0	Separated from strong oxidants, halogens.

IPCSInternational
Programme on
Chemical SafetyPrepared in the context of cooperation between the International
Programme on Chemical Safety and the European Commission
© IPCS 2000

SEE IMPORTANT INFORMATION ON THE BACK.

0457 **N,N-DIMETHYLFORMAMIDE**

IMPORTANT DATA

Physical State; Appearance

COLOURLESS TO YELLOW LIQUID, WITH CHARACTERISTIC ODOUR.

Chemical dangers

The substance decomposes on heating or on burning producing toxic fumes including nitrogen oxides.
Reacts violently with oxidants, nitrates and halogenated hydrocarbons. Attacks some plastic and rubber.

Occupational exposure limits

TLV: 10 ppm; (skin) (ACGIH 2000).
MAK: 10 ppm; 30 mg/m³; skin, Re2 (1999)

Routes of exposure

The substance can be absorbed into the body by inhalation and through the skin.

Inhalation risk

A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

Effects of short-term exposure

The substance is irritating to the eyes.
The substance may cause effects on the liver, resulting in jaundice. See Notes.

Effects of long-term or repeated exposure

The substance may have effects on the liver, resulting in impaired functions.
Animal tests show that this substance possibly causes toxic effects upon human reproduction.

PHYSICAL PROPERTIES

Boiling point: 153°C
Melting point: -61°C
Relative density (water = 1): 0.95
Solubility in water: miscible
Vapour pressure, Pa at 25°C: about 492
Relative vapour density (air = 1): 2.5

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.00
Flash point: 58°C c.c.
Auto-ignition temperature: 445°C
Explosive limits, vol% in air: 2.2-15.2 at 100°C
Octanol/water partition coefficient as log Pow: -0.87

ENVIRONMENTAL DATA

NOTES

Use of alcoholic beverages enhances the harmful effect.
Resulting symptoms could be delayed from several hours up to several days.
Environmental effects from the substance have been investigated, but none has been found.

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

Concise International Chemical Assessment Document 31**RÉSUMÉ D'ORIENTATION**

Ce CICAD sur le *N,N*-diméthylformamide (DMF) a été préparé conjointement par la Direction de l'hygiène du milieu de Santé Canada et la Direction de l'évaluation des produits chimiques commerciaux d'Environnement Canada, sur la base d'une documentation préparée simultanément dans le cadre du Programme d'évaluation des substances prioritaires, en application de la Loi canadienne sur la protection de l'environnement (LCPE). Les évaluations sanitaires des substances prioritaires effectuées en application de cette loi portent sur les effets que pourraient avoir ces produits sur la santé humaine en cas d'exposition indirecte dans l'environnement. L'exposition professionnelle n'est pas abordée dans le document de base. La présente mise au point prend en compte les données sur les effets environnementaux jusqu'à septembre 1999 et les données sur les effets sanitaires jusqu'à février 2000. L'appendice 1 donne des informations sur la nature de l'examen par des pairs et sur les sources documentaires. D'autres études ont également été utilisées, à savoir celle l'IARC/CIRC (1999) et celle du BUA (1994). Des renseignements sur l'examen par des pairs du présent CICAD sont donnés à l'appendice 2. Ce CICAD a été adopté en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Helsinki du 26 au 29 juin 2000. La liste des participants à cette réunion figure à l'appendice 3. La fiche internationale sur la sécurité chimique (ICSC 0457) du *N,N*-diméthylformamide, établie par le Programme international sur la sécurité chimique (IPCS, 1999), est également reproduite dans le présent document.

Le *N,N*-diméthylformamide (No CAS 68-12-2) est un solvant organique produit en grande quantité dans l'ensemble du monde. On utilise dans l'industrie chimique comme solvant, comme intermédiaire ou comme additif. Il se présente sous la forme d'un liquide incolore dégageant une faible odeur qui rappelle celle des amines. Il est miscible en toutes proportions à l'eau et à la plupart des solvants organiques. Sa tension de vapeur est relativement faible.

Une fois libéré dans l'air, le DMF y demeure en majeure partie jusqu'à décomposition par réaction avec des radicaux hydroxyles. La libération indirecte de DMF dans l'air, notamment à partir d'autres milieux, ne contribue guère au maintien de la concentration de ce composé dans le compartiment atmosphérique. On estime que le DMF présent dans l'air est photo-oxydé en l'espace de quelques jours. Une partie du DMF atmosphérique peut cependant atteindre le milieu aquatique ou terrestre, vraisemblablement à la faveur des précipitations. Le DMF qui passe dans l'eau subit une décomposition *in situ* sans transfert vers d'autres compartiments. Libéré dans le sol, il y demeure en

majeure partie - probablement dans l'eau des pores - jusqu'à dégradation par voie chimique ou biologique. En cas de décharge dans les eaux ou au sol, on peut s'attendre à une biodégradation relativement rapide (demi-vie de 18 à 36 h). Si le composé parvient jusqu'aux nappes souterraines, sa décomposition anaérobie sera lente. Compte tenu du mode d'utilisation du DMF, l'exposition de la population générale à ce composé est vraisemblablement très faible.

Etant donné que dans le pays témoin, la majeure partie du DMF est effectivement libérée dans l'air et compte tenu du devenir de ce composé dans l'environnement, l'exposition des organismes vivants est essentiellement atmosphérique et les organismes benthiques, comme ceux qui peuplent les eaux de surface ou le sol, sont sans doute peu exposés. Compte tenu de cela et étant donné la faible toxicité du DMF pour nombre d'organismes aquatiques ou terrioles, la caractérisation du risque vise essentiellement les organismes terrestres directement exposés au DMF présent dans l'air ambiant.

Le DMF est rapidement absorbé en cas d'exposition par voie orale, percutanée ou respiratoire. Une fois absorbé, le composé se répartit de façon uniforme dans l'organisme et après avoir été métabolisé principalement au niveau du foie, il est assez rapidement excrété par la voie urinaire sous la forme de métabolites. La principale voie métabolique consiste en une hydroxylation du groupement méthyle conduisant au *N*-(hydroxyméthyl)-*N*-méthylformamide (HMMF), qui est le principal métabolite urinaire chez l'Homme et l'animal. Le HMMF peut à son tour subir une décomposition en *N*-méthylformamide (NMF), dont l'hydroxylation enzymatique au niveau du groupement *N*-méthyle va entraîner la formation de *N*-(hydroxyméthyl)formamide (HMF), qui se décompose ensuite en formamide. Il existe également une possibilité de bifurcation métabolique à partir du NMF qui consiste en une oxydation du groupement formyle conduisant à la *N*-acétyl-*S*-(*N*-méthylcarbamoyl)cystéine (AMCC), métabolite dont on a décelé la présence dans l'urine humaine et l'urine de rongeurs. Au cours de ce processus, il se forme également un intermédiaire réactif dont la structure n'est pas encore élucidée (peut-être de l'isocyanate de méthyle). Bien qu'on ne dispose pas de preuve expérimentale directe, il se pourrait que ce composé soit le métabolite présumé toxique. À la lumière des données existantes, il semblerait que chez l'Homme, la proportion de DMF métabolisée par la voie présumée toxique soit plus importante que chez l'animal de laboratoire. Il existe une interaction métabolique entre le DMF et l'alcool, qui, bien qu'encore mal élucidée, pourrait être due à l'action inhibitrice de ce composé sur l'alcool-déshydrogénase.

Les données tirées d'analyses de cas individuels ou d'études transversales sur des populations professionnellement exposées, montrent, en accord avec

N,N-Dimethylformamide

les résultats de l'expérimentation animale, que chez l'Homme, c'est le foie qui est l'organe-cible du DMF. L'ensemble des effets correspond à ce qui s'observe chez l'animal de laboratoire, c'est-à-dire des troubles digestifs, une intolérance à l'alcool, l'augmentation du taux sérique des enzymes hépatiques (aspartate-amino-transférase, alanine-aminotransférase, γ -glutamyl-transpeptidase et phosphatase alcaline) accompagnés d'anomalies histopathologiques et de modifications ultrastructurales (nécrose hépatocellulaire, hypertrophie des cellules de Kupffer, stéatose microvésiculaire, lysosomes complexes, mitochondries pléomorphes et dégénérescence graisseuse avec présence occasionnelle de lipogranulomes).

A la lumière des données disponibles, il n'existe pas de faits probants ni cohérents qui témoignent d'une augmentation des tumeurs de toutes localisations imputable à l'exposition au DMF sur le lieu de travail. Les cas de cancer du testicule qui avaient été rapportés n'ont pas été confirmés par une étude de cohorte cas-témoins. Pour ce qui est d'autres localisations, aucune augmentation systématique de la fréquence tumorale n'a pu être associée à une exposition au DMF.

En ce qui concerne la génotoxicité du composé pour des populations professionnellement exposées, les données ne sont pas non plus très probantes ni cohérentes, les résultats des études effectuées sur des travailleurs exposés (au DMF et à d'autres composés) étant mitigés. L'ensemble des observations ne cadre pas avec les variations de l'exposition d'une étude à l'autre. Cependant, en raison de la relation dose-réponse positive observée lors de l'étude où cette possibilité avait été explorée, il s'agit là d'un domaine qui mériterait des études supplémentaires, même si les résultats obtenus dans des systèmes d'épreuve expérimentaux sont très largement négatifs en ce qui concerne la génotoxicité du DMF.

La toxicité aiguë du DMF est faible et il n'est que légèrement à modérément irritant pour les yeux et la peau. On n'a pas trouvé de données sur son pouvoir sensibilisateur. Les études de toxicité aiguë ou chronique par administration de doses répétées mettent invariablement en évidence l'hépatotoxicité du DMF, même aux concentrations ou aux doses les plus faibles. Au nombre des effets constatés figurent des modifications touchant les enzymes hépatiques qui sont caractéristiques d'une action toxique, l'augmentation du poids du foie, une dégénérescence histopathologique progressive pouvant conduire à la mort cellulaire et l'accroissement du taux sérique des enzymes hépatiques. Après avoir exposé des rats et des souris par la voie respiratoire et la voie orale, on a constaté l'existence d'une relation dose-réponse pour l'ensemble de ces effets. Par ailleurs, l'ordre de sensibilité des diverses

espèces relativement à ces effets est le suivant : souris > rat > singe.

La base de données relative à la cancérogénicité du DMF ne comporte en tout et pour tout que deux épreuves biologiques sur le rat et la souris, mais il en ressort néanmoins que l'inhalation prolongée de ce composé n'entraîne pas d'augmentation de l'incidence tumorale. Comme on l'a vu, les résultats des tests de génotoxicité sont très largement négatifs; ils proviennent d'études approfondies *in vitro*, consistant notamment à rechercher la présence de gènes mutés, ainsi que d'une base de données plus limitée constituée à partir d'épreuves *in vivo*.

L'expérimentation animale montre que le DMF n'a d'effets nocifs sur la reproduction qu'à des concentrations plus fortes que celles qui sont hépatotoxiques, après exposition tant par la voie respiratoire que par la voie orale. De même, lors d'études sur le développement bien conduites et publiées tout récemment, on n'a observé d'effets foetotoxiques et tératogènes systémiques qu'aux doses ou aux concentrations toxiques pour la mère.

Les données existantes sont insuffisantes pour permettre une évaluation des effets neurologiques et immunologiques du DMF.

Le présent CICAD et la caractérisation du risque que constitue le DMF ont essentiellement pour objet les effets de ce composé lors d'une exposition indirecte dans l'environnement.

C'est l'air au voisinage de sources ponctuelles de DMF qui fait courir à la population générale le risque d'exposition le plus important. D'après les études épidémiologiques effectuées sur des travailleurs exposés et les informations tirées de la base de données relativement fournie qui a été constituée à partir des résultats de l'expérimentation animale, c'est le foie qui constitue l'organe cible de l'action toxique du DMF. En se basant sur l'augmentation du taux sérique des enzymes hépatiques, on a fixé à 0,03 ppm (0,1 mg/m³) la concentration tolérable.

On n'a pas trouvé de données sur la toxicité du DMF pour les plantes vasculaires terrestres. Pour les indicateurs de sensibilité potentielle des arbres et des arbustes, les concentrations agissantes sont élevées, aussi est-il peu probable que les végétaux terrestres soient particulièrement sensibles à ce composé. En ce qui concerne les autres organismes terrestres, on est parvenu à une valeur de 15 mg/m³ pour la concentration sans effet en prenant la valeur limite pour l'hépatotoxicité chez la souris divisée par un coefficient d'application. En comparant cette valeur avec une estimation prudente de l'exposition on peut conclure que

Concise International Chemical Assessment Document 31

dans le pays témoin, le DMF n'a vraisemblablement aucun effet nocif sur les organismes terrestres.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre la *N,N*-dimetilformamida (DMF), preparado conjuntamente por la Dirección de Higiene del Medio del Ministerio de Salud del Canadá y la División de Evaluación de Productos Químicos Comerciales del Ministerio de Medio Ambiente del Canadá, se basó en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente* (CEPA). Las evaluaciones de sustancias prioritarias previstas en la CEPA tienen por objeto valorar los efectos potenciales para la salud humana de la exposición indirecta en el medio ambiente general, así como los efectos ecológicos. En este documento original no se abordó la exposición ocupacional. En este examen se analizaron los datos identificados hasta el final de septiembre de 1999 (efectos ecológicos) y febrero de 2000 (efectos en la salud humana). La información relativa al carácter del examen colegiado y la disponibilidad del documento original figura en el apéndice 1. También se consultaron otros exámenes, entre ellos el del IARC (1999) y el del BUA (1994). La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Helsinki (Finlandia) del 26 al 29 de junio de 2000. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0457) para la *N,N*-dimetilformamida, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1999), también se reproduce en este documento.

La *N,N*-dimetilformamida (CAS N° 68-12-2) es un disolvente orgánico que se produce en grandes cantidades en todo el mundo. Se utiliza en la industria química como disolvente, intermediario y aditivo. Es un líquido incoloro con un ligero olor a amina. Es completamente miscible con el agua y la mayoría de los disolventes orgánicos y su presión de vapor es relativamente baja.

Cuando se libera en el aire, la mayor parte de las emisiones de *N,N*-dimetilformamida se mantienen en este compartimento, donde se degrada por reacción química con radicales hidroxilo. Las emisiones indirectas de *N,N*-dimetilformamida al aire, por ejemplo por desplazamiento desde otros compartimentos del medio ambiente, desempeñan sólo una pequeña función en el mantenimiento de los niveles de *N,N*-dimetilformamida en la atmósfera. Se estima que la fotooxidación de la *N,N*-dimetilformamida en el aire dura unos días. Sin embargo, parte de la *N,N*-dimetilformamida atmosférica puede alcanzar los medios acuático y terrestre, posiblemente con la lluvia. Cuando se libera *N,N*-dimetilformamida en el agua, se degrada allí y no pasa a otros compartimentos. Cuando se libera al suelo, la mayor parte de

N,N-Dimethylformamide

la *N,N*-dimetilformamida se mantiene allí - posiblemente en el agua intersticial del suelo - hasta que se degrada por reacción biológica y química. Se supone que las emisiones al agua o al suelo van seguidas de una biodegradación relativamente rápida (semivida de 18-36 h). Si la *N,N*-dimetilformamida alcanza el agua freática, su degradación anaerobia será lenta. Las pautas de uso de la *N,N*-dimetilformamida hacen suponer que la exposición de la población general es probablemente muy baja.

Habida cuenta de que en el país de muestra la mayor parte de la *N,N*-dimetilformamida parece que se libera al aire y teniendo cuenta su destino en el medio ambiente, se supone que la biota está expuesta fundamentalmente a la *N,N*-dimetilformamida del aire; la exposición a la presente en las aguas superficiales, el suelo o los organismos bentónicos se supone que es escasa. Sobre esta base y debido a su baja toxicidad para una gran variedad de organismos acuáticos y del suelo, la caracterización del riesgo ambiental se concentra en los organismos terrestres expuestos directamente a la *N,N*-dimetilformamida del aire ambiente.

La *N,N*-dimetilformamida se absorbe fácilmente tras la exposición oral, cutánea o por inhalación. Después de la absorción, la *N,N*-dimetilformamida se distribuye de manera uniforme, se metaboliza sobre todo en el hígado y se excreta con relativa rapidez como metabolitos en la orina. En la vía principal interviene la hidroxilación de los grupos metilo, produciendo *N*-(hidroximetil)-*N*-metilformamida, que es el principal intermediario urinario en las personas y en los animales. La *N*-(hidroximetil)-*N*-metilformamida se puede descomponer a su vez para formar *N*-metilformamida. Luego, la oxidación enzimática del *N*-metilo de la *N*-metilformamida puede dar lugar a *N*-(hidroximetil)formamida, que a continuación se degrada a formamida. Una vía alternativa para el metabolismo de la *N*-metilformamida es la oxidación del grupo formilo, produciendo *N*-acetil-*S*-(*N*-metilcarbamoil)-cisteína, que ha sido identificado como un metabolito urinario en los roedores y en las personas. En esta vía se forma un intermediario reactivo, cuya estructura aún no se ha determinado (posiblemente metilisocianato); aunque no se han encontrado pruebas experimentales directas que lo respalden, parece que este intermediario es el metabolito supuestamente tóxico. Los datos disponibles indican que la proporción de *N,N*-dimetilformamida que se puede metabolizar por la vía supuestamente tóxica es mayor en las personas que en los animales de experimentación. Se ha detectado una interacción metabólica entre la *N,N*-dimetilformamida y el alcohol, lo cual, aunque no se conoce del todo, se puede deber, al menos en parte, a que inhibe la alcohol deshidrogenasa.

Coincidiendo con los resultados de los estudios en animales de experimentación, los datos disponibles de informes de casos y de estudios de muestras represen-

tativas de poblaciones expuestas ocupacionalmente indican que en las personas es el hígado el órgano destinatario de la toxicidad de la *N,N*-dimetilformamida. El perfil de los efectos está en consonancia con el observado en los animales de experimentación, habiéndose detectado trastornos gastrointestinales, intolerancia al alcohol, aumento de las enzimas hepáticas en el suero (aspartato aminotransferasa, alanina aminotransferasa, (-glutamyl transpeptidasa y fosfatasa alcalina) y efectos histopatológicos y cambios ultraestructurales (necrosis hepatocelular, agrandamiento de las células de Kupffer, esteatosis microvesicular, lisosomas complejos, mitocondrias pleomórficas y cambios en la grasa con lipogranulomas ocasionales).

Teniendo en cuenta los limitados datos disponibles, no hay pruebas sistemáticas convincentes de un aumento del número de tumores en los lugares asociados con la exposición a la *N,N*-dimetilformamida en el entorno ocupacional. Las notificaciones de casos de cáncer testicular no se han confirmado en un estudio de cohortes y de casos y testigos. No se ha observado un aumento constante de tumores en otros lugares asociados con la exposición a la *N,N*-dimetilformamida.

Hay también pocas pruebas sistemáticas convincentes de genotoxicidad en las poblaciones expuestas ocupacionalmente a la *N,N*-dimetilformamida, con resultados desiguales en los estudios disponibles sobre trabajadores expuestos (a la *N,N*-dimetilformamida y a otros compuestos). La pauta de las observaciones no es coherente con las variaciones de la exposición en los diversos estudios. Sin embargo, a la vista de la relación dosis-respuesta positiva observada en el único estudio en el cual se investigó, convendría estudiar más este aspecto, aunque los datos disponibles sobre genotoxicidad en sistemas experimentales son abrumadoramente negativos.

La *N,N*-dimetilformamida tiene una toxicidad aguda baja y una actividad irritante ocular y cutánea entre ligera y moderada. No se identificaron datos relativos a su potencial de sensibilización. En estudios de toxicidad aguda y de dosis repetidas, la *N,N*-dimetilformamida ha sido siempre hepatotóxica, induciendo efectos en el hígado a las concentraciones o dosis más bajas. El perfil de los efectos incluye alteraciones en las enzimas hepáticas características de la toxicidad, aumento de peso del hígado, cambios histopatológicos de degeneración progresiva y a la larga muerte celular, así como aumento de las enzimas hepáticas en el suero. Tras la exposición por inhalación y por vía oral se ha observado una relación dosis-respuesta para estos efectos en ratas y ratones. Se ha detectado una variación de la sensibilidad entre especies para estos efectos, siendo el orden de sensibilidad ratones > ratas > monos.

Aunque la base de datos para la carcinogenicidad se limita a dos biovaloraciones debidamente realizadas en ratas y ratones, no se ha registrado un aumento de la incidencia de tumores tras la exposición por inhalación crónica a la *N,N*-dimetilformamida. El valor probatorio para la genotoxicidad es totalmente negativo, basándose en una investigación amplia mediante valoraciones *in vitro*, en particular para la mutación genética, y en una base de datos más limitada *in vivo*.

En estudios con animales de laboratorio, tras la exposición tanto por inhalación como por vía oral la *N,N*-dimetilformamida indujo efectos reproductivos adversos sólo a concentraciones superiores a las asociadas con los efectos adversos en el hígado. Del mismo modo, en estudios fundamentalmente recientes sobre el desarrollo realizados y notificados de manera adecuada, se han observado sistemáticamente efectos citotóxicos y teratogénicos sólo a concentraciones o dosis con toxicidad materna.

Los estudios disponibles no son suficientes como base para la evaluación de los efectos neurológicos e inmunológicos de la *N,N*-dimetilformamida.

Este CICAD y la caracterización del riesgo en la muestra se concentran fundamentalmente en los efectos de la exposición indirecta en el medio ambiente general.

El aire en la proximidad de fuentes puntuales parece ser el principal origen potencial de exposición de la población general a la *N,N*-dimetilformamida. Sobre la base de los resultados de los estudios epidemiológicos de trabajadores expuestos y de los datos justificativos de una base de datos relativamente amplia de investigaciones en animales de experimentación, el hígado es el principal órgano destinatario de la toxicidad de la *N,N*-dimetilformamida. Se ha obtenido una concentración tolerable de 0,03 ppm (0,1 mg/m³), teniendo en cuenta el aumento de las enzimas hepáticas en el suero.

No se han identificado datos sobre la toxicidad de la *N,N*-dimetilformamida para las plantas vasculares terrestres. Las concentraciones con efecto para los indicadores de una posible sensibilidad de los árboles, los arbustos y otras plantas son altas; por consiguiente, es poco probable que las plantas terrestres sean particularmente sensibles a la *N,N*-dimetilformamida. Para otros organismos terrestres, se ha estimado un valor sin efectos de 15 mg/m³, basado en un valor crítico de la toxicidad para la toxicidad hepática en ratones dividido por un factor de aplicación. La comparación de este resultado con un valor de exposición estimada prudente indica que es poco probable que la *N,N*-dimetilformamida provoque efectos adversos en los organismos terrestres del país de muestra.

THE CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENT SERIES

Azodicarbonamide (No. 16, 1999)
Benzoic acid and sodium benzoate (No. 26, 2000)
Benzyl butyl phthalate (No. 17, 1999)
Biphenyl (No. 6, 1999)
1,3-Butadiene: Human health aspects (No. 30, 2001)
2-Butoxyethanol (No. 10, 1998)
Chloral hydrate (No. 25, 2000)
Crystalline silica, Quartz (No. 24, 2000)
Cumene (No. 18, 1999)
1,2-Diaminoethane (No. 15, 1999)
3,3'-Dichlorobenzidine (No. 2, 1998)
1,2-Dichloroethane (No. 1, 1998)
2,2-Dichloro-1,1,1-trifluoroethane (HCFC-123) (No. 23, 2000)
Diphenylmethane diisocyanate (MDI) (No. 27, 2000)
Ethylenediamine (No. 15, 1999)
Ethylene glycol: environmental aspects (No. 22, 2000)
2-Furaldehyde (No. 21, 2000)
HCFC-123 (No. 23, 2000)
Limonene (No. 5, 1998)
Manganese and its compounds (No. 12, 1999)
Methyl chloride (No. 28, 2000)
Methyl methacrylate (No. 4, 1998)
Mononitrophenols (No. 20, 2000)
Phenylhydrazine (No. 19, 2000)
N-Phenyl-1-naphthylamine (No. 9, 1998)
1,1,2,2-Tetrachloroethane (No. 3, 1998)
1,1,1,2-Tetrafluoroethane (No. 11, 1998)
o-Toluidine (No. 7, 1998)
Tributyltin oxide (No. 14, 1999)
Triglycidyl isocyanurate (No. 8, 1998)
Triphenyltin compounds (No. 13, 1999)
Vanadium pentoxide and other inorganic vanadium compounds (No. 29, 2001)

*To order further copies of monographs in this series, please contact Marketing and Dissemination,
World Health Organization, 1211 Geneva 27, Switzerland
(Fax No.: 41-22-7914857; E-mail: bookorders@who.int)*

Exhibit 25

INTERNATIONAL UNION OF
PURE AND APPLIED CHEMISTRY

ANALYTICAL CHEMISTRY DIVISION
COMMISSION ON ELECTROANALYTICAL CHEMISTRY

DIMETHYLFORMAMIDE: PURIFICATION,
TESTS FOR PURITY AND PHYSICAL
PROPERTIES

Prepared for publication by
JEAN JUILLARD

Laboratoire d'Etude des Interactions Solutés-Solvants,
Université de Clermont—B.P. 45—63170 Aubière, France

February 8, 2023

EXHIBIT
AFNAN

007

PERGAMON PRESS
OXFORD • NEW YORK • PARIS • FRANKFURT

Analytical Chemistry Division

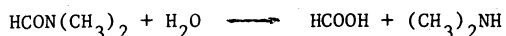
Commission on Electroanalytical Chemistry

DIMETHYLFORMAMIDE: PURIFICATION, TESTS FOR PURITY AND PHYSICAL PROPERTIES[†]

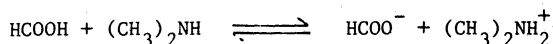
N,N'-Dimethylformamide (DMF) is a good solvent for organic and to a lesser extent inorganic compounds. It is, together with dimethylsulfoxide and acetonitrile, one of the most widely used of the so-called dipolar aprotic solvents. Owing to its fairly high dielectric constant, it is a moderately dissociating solvent for electrolytes. Acid-base reactions as well as thermodynamic properties of electrolyte solutions have been studied by many authors. Contrary to the N-methylamides it is a typically weakly associated solvent, as seen (Ref. 1) from dielectric studies (the Kirkwood g factor is about one at all temperatures).

Owing to its electron-donor character, DMF reacts with many acids. For example, Gutmann's donicity number (Ref. 2) is 27. Its polarographic range is quite large, e.g., 3.5 V at the dropping mercury electrode with 0.1 M Bu₄NC10₄ as supporting electrolyte (Ref. 3). It is therefore widely used as a solvent for electrochemical reactions, especially reductions.

Pure DMF is colorless and, at room temperature, odorless. It is subject to thermal as well as photochemical degradation. In presence of water, DMF is slowly hydrolyzed according to the equation:



Formic acid and dimethylamine are thus predominant impurities in DMF and determine the odor of the impure solvent. They are weakly acidic and weakly basic respectively; therefore, partial ionization does occur:



and results in a buffered solution (pH 11) with an increase in the conductivity of the solution.

Thermal degradation produces dimethylamine and carbon monoxide. Hydrogen (Ref. 4) and hydrogen cyanide (Ref. 5) have been identified among the products of the photochemical degradation of the solvent.

Strongly basic media are difficult to obtain in DMF; there is, to our knowledge, no substance behaving as a strong base in DMF. If autoprotolysis of the medium actually occurs, the anion of the solvent must be very unstable (Ref. 6). It has been claimed (Ref. 7 and 8) that the autoprotolysis constant is smaller than 10⁻²⁵ but no definite value has yet been proposed.

Attention must be paid to the fact that DMF has toxic effects, particularly on the liver and kidneys; the threshold value for air has been fixed (Ref. 9) at 30 mg/m³.

PURIFICATION OF DIMETHYLFORMAMIDE

Good quality DMF is commercially available. As noted by Vaughn (Ref. 10), spectrograde solvent is not always suitable for all purposes. As a consequence of hydrolysis, the residual water content of commercial DMF is frequently low (0.1%). Many procedures have been proposed and used for the purification of the solvent. Four types of successive operation can be distinguished: treatment with a drying agent, neutralization of basic or acidic impurities, careful distillation, and elimination of gaseous impurities.

[†] Titular Members: R. G. Bates, Chairman (USA); J. F. Coetzee, Secretary, (USA); Members: E. Bishop (UK), T. Fujinaga (Japan), Z. Galus (Poland), J. Jordan (USA), H. W. Nürnberg (FRG), P. Zuman (USA); Associate Members: M. Branica (Yugoslavia), A. K. Covington (UK), L. Gierst (Belgium), K. Izutsu (Japan), L. Meites (USA), E. Pungor (Hungary), O. A. Songina (USSR), B. Trémillon (France); National Representatives: D. D. Perrin (Australia), G. Kraft (FRG), R. C. Kapoor (India), N. Tanaka (Japan), W. Kemula (Poland), P. O. Kane (UK).

1. Preparing water-free solvent. Although the boiling point of water is far from that of DMF it is not possible to obtain a dry solvent by distillation only.

One of the first methods proposed for preliminary drying (Ref. 11) was azeotropic distillation with about 10% by volume of dry benzene; the benzene-water azeotrope is removed by distillation at atmospheric pressure. To prevent decomposition the temperature is maintained below 80°C. Alternatively, molecular sieves can be used. The solvent is kept in contact for periods ranging from 1 to 4 days with 4 Å (Ref. 12-15) or 5 Å (Ref. 16) sieves which are removed and replaced from time to time. Ritchie (Ref. 17) recommends the use of Linde AW-500 molecular sieves in 1/16-inch pellets. Studying drying efficiency, he finds that the water content is less than 18 ppm after 27 hours. Molecular sieves can be dried before use by heating in a quartz tube under a stream of argon at 375°C for 24 h (Ref. 18). Finally, a procedure which uses chromatographic purification through alumina has been described by Moe (Ref. 13) in some detail. "A column approximately 100 cm long and 5 cm wide will contain 1 kg of alumina, sufficient for the purification of about 10 l of DMF". After bubbling of pure nitrogen for several hours the DMF thus obtained is thought to be convenient for polarographic use.

In our opinion these three types of operation can be considered only as a first step in drying the solvent, and mild chemical drying agents must also be used. These range from anhydrous BaO (Ref. 11 and 19) to MgSO₄ (Ref. 20), Na₂CO₃ (Ref. 6 and 20), or CuSO₄ (Ref. 21). Surprisingly good samples of DMF can be obtained using storage of solvent over these chemicals for at least 24 h. It has been recommended that the drying agent be changed at least twice and the container shaken, if not continuously, at least from time to time. It also has been recommended that such an operation is performed in a cold, dark room. As far as Na₂SO₄ or Na₂CO₃ are concerned, the resulting solvents are of about the same quality (Ref. 20). Little or no degradation of the solvent (as estimated through the concentration of dimethylamine) results from such treatment (Ref. 11).

Some of the more common drying agents react with the solvent itself to produce significant amounts of acidic or basic impurities. BaO, cited previously, belongs to this category if it is used at temperatures above 30°C (Ref. 11). Other reagents are potassium hydroxide, calcium hydride (Ref. 5 and 22) and phosphorus pentoxide (Ref. 17, 23 and 24). P₂O₅ is the most frequently used, CaH₂ is probably the most efficient. Prue and Sherrington (Ref. 23) have shaken DMF for three days with P₂O₅, adding each morning about 10 g of fresh reagent. Recently, drying of amides using Vitrid, sodium bis(methoxy-2-ethoxy)aluminumhydride, has been recommended (Ref. 25). In DMF it allows attainment of very basic media (pH 30). However, distillation of the solvent from the mixture obtained has not been attempted and is probably very hazardous. Whatever the method used, it is important to proceed with these operations in a dark room or apparatus to prevent any photochemical degradation.

2. Neutralization. Depending on the drying agent used, it has been recommended that the basic or acidic impurities produced are neutralised, either by shaking with picric acid (Ref. 20) or KOH pellets (Ref. 24). This last treatment is particularly recommended after drying over P₂O₅ which generates formic acid. Such neutralization can be done either before or after a first distillation.

3. Distillation. The drying process can be further carried out during this operation. The DMF is refluxed and distilled from P₂O₅ or CaH₂. However, owing to a degradation process increased by heating, it is preferable first to decant the solvent and transfer it under dry nitrogen, and then to distil it at reduced pressure.

The quality of the final product is greatly affected by the care with which the distillation is carried out. It seems to be important to work under vacuum, with a darkened column, or in a pure nitrogen or argon atmosphere. As a rule, the temperature must be kept under 60°C; heating must be gentle and overheating avoided. Distillation in daylight results in the production of hydrogen cyanide (Ref. 5), particularly in the presence of CaH₂. No traces of HCN are detected if the operations are conducted in the dark.

Types of distillation apparatus currently described in the literature do not seem to be very efficient. It is not surprising to note that the best quality DMF, if conductivity is accepted as a test of purity, has been obtained by Brummer (Ref. 12), who used only molecular sieves as drying agents, but carried out the distillation in a slow current of dry nitrogen at low pressure (2 torr) and an efficient column (1 meter packed with Fenske helices). The use of a long column (60 cm at least) with good packing and reflux is recommended. For example, Tanaka (Ref. 21) distilled DMF which had been dried over anhydrous CuSO₄ at a pressure of 5 torr through an adiabatic fractional distillation column which was 1.3 cm in diameter, 120 cm in length and packed with helipack coils. Dry nitrogen was passed through the apparatus during the distillation; 60% of the distillate was collected. The conductivity was lower than $1 \times 10^{-7} \Omega^{-1} \text{ cm}^{-1}$ (25°C). Boiling temperatures at various pressures are given in Table 1.

TABLE 1. Recommended values for physical constants of DMF at 25°C and 1 atm (except where noted otherwise)

Boiling temperature	T_B	152.3°C (Ref. 47)
		79°C at 61–62 torr (Ref. 37)
		55–56°C at 25–26 torr (Ref. 40)
		34°C at 2–3 torr (Ref. 15)
Melting temperature	T_M	-61°C
Refractive index (Ref. 44)	n_D^{25}	1.42689
Dielectric constant	D	37.0
Surface tension (Ref. 45)	σ	37.1 dyne/cm
Viscosity (Ref. 23)	η	0.00796 poise
Density	ρ	0.9440 g cm ⁻³
Molal volume	V	77.39 cm ³
Heat capacity at constant pressure (Ref. 44)	C_p	37.4 cal/mol
Cubic expansion coefficient	α_p	1.00 x 10 ⁻³ K ⁻¹ *
Adiabatic compressibility coefficient (Ref. 44)	β_s	6.1 x 10 ⁻⁵ atm ⁻¹
Isothermal compressibility coefficient	β_T	6.3 x 10 ⁻⁵ atm ⁻¹ *

* Calculated from data in Ref. (12)

4. Elimination of gaseous impurities. A flow of pure dry nitrogen or argon is passed through the solvent for several hours, in order to eliminate oxygen, carbon monoxide and carbon dioxide. Such a solvent can then be used for polarographic purposes. A more complete deaeration can be achieved using a vacuum line.

5. Conclusions and recommendations. As various authors used different starting materials, it is difficult to compare the efficiency of the various methods of purification. Comparison between different ways of treating the same batch of solvent can be found to our knowledge in only two papers (Ref. 11 and 20). Thomas and Rochow (Ref. 11) always used first azeotropic distillation with benzene and compared subsequent treatment with MgSO₄, BaO, alumina and triphenylchlorosilane, followed in each case by distillation. Comparisons were made in terms of specific conductance and water content. Barium oxide as well as alumina treatment meet rather well these two criteria and do not have any side effects, such as producing dimethylamine or HCN. Juillard (Ref. 20) compared drying with Na₂CO₃, Na₂SO₄ or molecular sieves with azeotropic distillation with benzene and distillation over P₂O₅. As far as conductivity and water content are concerned, the different batches of solvent thus obtained were of about the same quality, except that P₂O₅ has the disadvantage of promoting degradation of the solvent and thus of decreasing the efficiency of the distillation; therefore the use of P₂O₅ is not recommended. As a confirmation it can be noted that authors using P₂O₅ or CaH₂ as drying agents did not obtain purer solvents than those who employed BaO or Na₂CO₃ or even only molecular sieves.

It is therefore recommended that use is made first either of azeotropic distillation with benzene, as suggested by Thomas (Ref. 11), or of treatment with molecular sieves, as suggested by Ritchie (Ref. 17), and that the resulting DMF is then shaken with Na₂CO₃ or, better, with BaO for 1 or 2 days. After decantation the DMF is distilled twice under nitrogen (pressure <15 torr) using a 1-m column. All these operations must be carried out in the dark. After deaeration the solvent is stored under nitrogen and used as soon as possible.

TESTS FOR PURITY

Owing to its various modes of degradation (hydrolysis, thermal and photochemical decomposition) the principal impurities found in DMF are: dimethylamine, formic acid, hydrogen cyanide, carbon dioxide and carbon monoxide. To this list must be added: water, oxygen, which is quite soluble, and impurities resulting from the purification process.

Conductivity. As stressed earlier, hydrolysis as well as decomposition results in ionic impurities: dimethylammonium formate, carbonate or cyanide. Thus, the conductivity of the solvent is a very good test of its purity.

Experimental conductivities recorded in DMF are always higher than those reported for other aprotic solvents such as ketones or nitriles. According to a rough estimate, the theoretical conductivity of the solvent should be below $10^{-13} \Omega^{-1}\text{cm}^{-1}$. In fact, conductivities obtained by the most careful workers are scarcely ever less than 10^{-7} . The best values have been reported, to our knowledge, by Brummer (Ref. 12) who used for conductometric studies a solvent having conductivities varying from 2×10^{-8} to $5 \times 10^{-8} \Omega^{-1} \text{cm}^{-1}$. Values below 5×10^{-7} have been reported by numerous authors and any batch of DMF which is more conducting can be considered to be impure.

Water. Water can be titrated by the Karl Fischer (K-F) reagent. Kanatharan (Ref. 22) recommends that the titration is conducted slowly, since K-F reagent reacts only slowly with small amounts of water.

Usual procedures do not allow the determination of less than 10 ppm of water. According to Muroi (Ref. 26) it is possible to titrate as little as 0.2 ppm by increasing the sharpness of the end point, using the following procedure: "Add a 10-30 ml sample to 25 ml MeOH containing 8% of a pyridine- SO_2 solution (320 g SO_2 /l pyridine) and titrate potentiometrically with K-F reagent having a titre of 0.1-0.5 mg $\text{H}_2\text{O}/\text{ml}$ ". The use of DMF as a solvent for K-F reagent also has been advocated (Ref. 27).

Prue (Ref. 23) has titrated water in DMF using triphenylsilyl chloride, from which, according to Thomas (Ref. 11), hydrogen chloride is liberated quantitatively by water (amines or acids are thought to interfere); the HCl content is then estimated from the conductivity of the solution.

It is quite easy to prepare a solvent which contains less than 50 ppm of water. Very low concentrations ($< 5\text{ppm}$) are more difficult to attain. The best value, less than 3 ppm, has been reported by Libbey and Stock (Ref. 28).

Dimethylamine. Colorimetric methods have been used by some authors. In our opinion, as long as the autoprotolysis constant of the solvent is not known, it is not possible to say exactly what is basic and what is acidic in DMF. Kolthoff (Ref. 24) has used p-nitrophenol in the colorimetric determination of total basicity, but specific determinations would be preferable.

Thomas and Rochow (Ref. 11) have based the determination of the amine content on the fact that dimethylamine forms with 1-fluoro-2,4-dinitrobenzene a complex which absorbs in the visible spectrum at 3812 Å. Solvent prepared by Chang and Criss (Ref. 29) was found to contain less than 1 ppm of dimethylamine using this method.

Another spectrophotometric method which allows the determination of the dimethylamine content down to 2 ppm with an error of $\pm 10\%$ has been proposed by Pribyl (Ref. 30); dimethyldithiocarbamate, which absorbs at 445 nm, is formed by adding CS_2 and $\text{Cu}(\text{AcO})_2$ to an EtOH-pyridine mixture.

Chromatography was thought by Butler (Ref. 18) not to be a reliable means of establishing the organic impurity content of the solvent since DMF can decompose or hydrolyze at high temperatures. Nevertheless, careful studies of the proper experimental conditions have been undertaken (Ref. 31 and 32). In the paper by Filippov (Ref. 32) it is shown that dimethylamine can be determined in DMF at levels as low as 1 ppm using tetrahydroxyethylenediamine as a stationary phase, polysorb-1 as a solid support and a column temperature of 75°C .

Dimethylamine is not electroactive with mercury but can give coordination compounds with cations which will affect the course of electrochemical reductions.

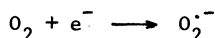
Formic Acid. In contrast to dimethylamine, formic acid is electroactive. Kanatharan and Spritzer (Ref. 22) have attributed to formic acid two peaks, one cathodic, the other anodic, which appear in cyclic voltammograms of aqueous dimethylformamide. Alternating current polarography (Ref. 33), and, better, pulse polarography, can be used to estimate the formic acid content.

Formic acid can also be determined by titration with a base. Potentiometric titration is preferred since it allows determination of the dimethylammonium formate content as well. Megliskii (Ref. 34) has titrated potentiometrically formic acid, dimethylamine and dimethylammonium formate in DMF using two solutions: 0.1 M HClO₄ and 0.1 M KOH, both in alcohol. Such a method is suitable only for concentrations of the order of at least 100 ppm.

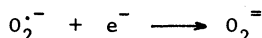
Hydrogen Cyanide. Trisler et al. (Ref. 5) reported the presence of HCN in DMF distilled over CaH₂ in natural light. Concentrations ranged from 10⁻⁵ to 10⁻³ M. Spectrophotometric titration can be carried out with 4-nitrobenzil, which reacts with cyanide ion to form a deep violet ion.

Oxygen. Oxygen is rather soluble in DMF. A study of oxygen solubility in relation to the oxygen content of the gas phase has been made by James (Ref. 35). When the gas phase was air and pure oxygen, the solubility was 2.2 x 10⁻³ and 3.1 x 10⁻³ M, respectively.

Oxygen is an electroactive impurity which interferes in polarography and other electrochemical processes. Two waves are observed (Ref. 36) with E_{1/2} = -0.8 and -2.8 V vs. SCE; the first corresponds to the reduction of oxygen to superoxide:



and the second one to the reduction of superoxide to peroxide ion:



James (Ref. 35) has proposed two methods for the determination of the oxygen concentration; polarography and the Winkler method. Polarographic measurements are made at -1.2 V vs. SCE, in order to ensure that the measured diffusion current is not influenced by a polarographic maximum. A modified Winkler method allows concentrations as low as 10 ppm to be determined. It depends upon quantitative oxidation of iodide ion to iodine. Such a process is described in some detail (Ref. 35).

PHYSICAL PROPERTIES OF DIMETHYLFORMAMIDE

Numerical values of physical constants are highly dependent on the purity of the solvent. Consequently, important discrepancies are found in the literature. The present recommended values result from a careful examination of three aspects: accuracy of the measurements, consistency of the data of various authors at different temperatures, and purification of the solvent. Such a choice is subject to personal evaluation and it seems prudent to give also the other references.

Density. The density is probably a good criterion of the purity of the solvent. Contamination with water increases the density (Ref. 23). The following values of the density at 25°C have been found (Ref. 23,8,37,12): 0.9439, 0.9440₂, 0.9441₅ and 0.9442 g cm⁻³, respectively. Old values greater than 0.9443 frequently found in tables are probably too high. New work by Kawaizumi and Zana (Ref. 38) seems to indicate that the density of the pure solvent is lower. These authors obtain values ranging from 0.94360 to 0.94368. It is our feeling that these data are more accurate than previous ones but such a low value (ρ = 0.94364 ± 0.00004) must be confirmed by others before being accepted.

Values at various temperatures other than those appearing in Table 2 have been given by Gopal and Rizvi (Ref. 39). At 20°C Saphon (Ref. 40) has obtained ρ = 0.94878 g cm⁻³, in good agreement with the value in Table 2.

TABLE 2. Recommended values for physical constants of DMF at various temperatures

		ρ g cm ⁻³	η poise	D
Temperature	20°C	0.9488	0.00845	38
	30°C	0.9394	0.00746	36.1
	40°C	0.9298	0.00664	34.4
	50°C	0.9202	0.00598	32.8
Reference		12	49	1

Viscosity. Other values can be found in References (29) and (41). Prue's data at 25°C are confirmed by measurements reported by Ames and Sears (Ref. 42).

Dielectric constant. Data given by Bass and Cole (Ref. 1) are preferred to previous results (Ref. 43) of Leader and Gormley (36.71 at 25°C). The value reported at 25°C is interpolated from measurements at various temperatures. Data of Saphon (Ref. 40) are in good agreement with the value reported in Table 2 at 20°C ($D = 38.13$).

Miscellaneous. Data at various temperatures concerning refractive index, surface tension and isothermal compressibility can be found in Refs. (44), (45) and (12), respectively. Other data concerning thermodynamic properties are reported in Refs. (39) and (44). Plots of vapor pressure, heat of vaporization, heat capacity, density, viscosity, surface tension and thermal conductivity for a large range of temperature have been drawn up by Gallant (Ref. 46). The solubilities of some sixty substances in DMF have been tabulated (Ref. 50). Organic reactions in or with DMF have been summarized (Ref. 51).

REFERENCES

1. S. J. Bass, V. I. Nathan, R. M. Meigham and R. H. Cole, *J. Phys. Chem.*, **68**, 1509 (1964).
2. V. Gutmann, *Coordination Chemistry in Non-Aqueous Solutions*, Springer Verlag (1968), p. 152.
3. M. Bréant, M. Bazouin, C. Buisson, M. Dupin and J. M. Rebattu, *Bull. Soc. Chim. France*, 5065 (1968).
4. J. Kroh, E. Burzynska, *Bull. Acad. Polon. Sci., Sc. Chim.*, **21**, 289 (1973).
5. J. C. Trisler, B. F. Freasier and Shi-Ming Wu, *Tetrahedron Letters*, 687 (1974).
6. Ram Chand Paul, P. S. Guraya and B. R. Sreenathan, *Indian J. Chem.*, **1**, 335 (1963).
7. M. Bréant and G. Demange-Guérin, *Bull. Soc. Chim. France*, 2935 (1969).
8. E. Lolette and J. Juillard, *J. Sol. Chem.*, **3**, 127 (1974).
9. H. E. Stokinger, *Documentation of Threshold Limit Values*, revised ed., American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio (1966).
10. J. W. Vaughn in *The Chemistry of Non-Aqueous Solvents*, ed. J. J. Lagowski, Academic Press, New York (1967) Vol. II, p. 243.
11. A. P. Thomas and E. G. Rochow, *J. Amer. Chem. Soc.*, **79**, 1843 (1957).
12. S. B. Brummer, *J. Chem. Phys.*, **42**, 1636 (1965).
13. N. S. Moe, *Acta Chem. Scand.*, **21**, 1389 (1967).
14. S. C. Chan and J. P. Valteau, *Can. J. Chem.*, **46**, 853 (1968).
15. D. A. Owensby, A. J. Parker and J. W. Diggle, *J. Amer. Chem. Soc.*, **96**, 2682 (1974).
16. J. N. Butler, *J. Phys. Chem.*, **72**, 3288 (1968).
17. C. D. Ritchie and G. H. Megerle, *J. Amer. Chem. Soc.*, **89**, 1447 (1967).
18. J. N. Butler, *J. Amer. Chem. Soc.*, **92**, 2602 (1970).
19. O. N. Bhatnager and C. M. Criss, *J. Phys. Chem.*, **73**, 174 (1969).
20. J. Juillard, *J. Chim. Phys.*, **67**, 691 (1970).
21. N. Tanaka, personal communication.
22. P. Kanatharan and M. S. Spritzer, *Anal. Letters*, **6**, 421 (1973).
23. J. E. Prue and P. J. Sherrington, *Trans. Faraday Soc.*, **57**, 1795 (1961).
24. I. M. Kolthoff, M. K. Chantooni, Jr., and H. Smagowski, *Anal. Chem.*, **42**, 1622 (1970).
25. M. Bréant, *Journées d'Electrochimie*, Rouen (France), 10 Avril 1975; M. Bréant and J. Georges, *C. R. Acad. Sc. Paris, Série C* **280**, 33 (1975).
26. K. Muroi, M. Ono, *Bunseki Kagaku*, **20**, 975 (1971).
27. V. A. Klimova, F. B. Sherman and A. M. L'vov, *Isvest. Akad. Nauk SSSR, Ser. Khim.*, 2599 (1967).
28. A. J. Libbey and J. T. Stock, *Anal. Chem.*, **42**, 526 (1970).
29. S. Chang and C. M. Criss, *J. Sol. Chem.*, **2**, 457 (1973).
30. N. Pribyl and J. Nedbalkova, *Fresenius'Z. Anal. Chem.*, **232**, 261 (1967).
31. V. A. Zverev and G. A. Krestov, *Isv. Vyssh. Uchebn. Zavedeni, Khimiya i Khim: Tekhnol.*, 963 (1968).
32. Yu S. Filippov and Ya A. Tsarfin, *Zh. Anal. Khim.*, **26**, 1644 (1971).
33. A. Francina, *Thèse Docteur-ès-Sciences*, Lyon (France), 1973, p. 72.
34. V. A. Meglitskii and N. n. Kvasha, *Khim. Volokna*, 70 (1971).
35. H. J. James and R. F. Broman, *Anal. Chim. Acta.*, **48**, 411 (1969).
36. D. L. Maricle and W. G. Hodgson, *Anal. Chem.*, **37**, 1562 (1965).
37. C. M. French and K. H. Glover, *Trans. Faraday Soc.*, **51**, 1418 (1955).
38. Personal communication of numerical values used in the paper by F. Kawaizumi and R. Zana, *J. Phys. Chem.*, **78**, 1099 (1974).
39. Ram Gopal and S. A. Rizvi, *J. Indian Chem. Soc.*, **43**, 179 (1966).
40. S. Saphon and H. J. Bittlich, *Z. Phys. Chem., Leipzig*, **252**, 113 (1973).
41. Ram Gopal and P. P. Rastogi, *Z. Phys. Chem. N.F. (Frankfurt)*, **69**, 1 (1970).
42. D. P. Ames and P. G. Sears, *J. Phys. Chem.*, **59**, 16 (1955).
43. G. R. Leader and J. F. Gormley, *J. Amer. Chem. Soc.*, **73**, 5731 (1951).
44. B. E. Geller, *Zh. Fiz. Khim.*, **35**, 2110 (1961).
45. R. A. Stairs, W. T. Rispin and R. C. Makhija, *Can. J. Chem.*, **48**, 2755 (1970).
46. R. W. Gallant, *Hydrocarbon Processing*, **48**, 199 (1969).
47. B. V. Ioffe, *Zh. Obshch. Khim.*, **25**, 902 (1955).
48. J. R. Ruhoff and E. E. Reid, *J. Amer. Chem. Soc.*, **59**, 4012 (1937).
49. L. R. Dawson and W. W. Wharton, *J. Electrochem. Soc.*, **107** 700 (1960).
50. Ram Chand Paul and B. R. Sreenathan, *Ind. J. Chem.*, **4**, 382 (1966).
51. R. S. Kittila, *Dimethylformamide: Chemical Uses*, E. I. duPont de Nemours and Co. (1967).

Exhibit 27

Theoretical Investigation of *N*-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine

Zhi Sun, Yong Dong Liu,* and Ru Gang Zhong

College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, R. P. China

Received: June 16, 2009; Revised Manuscript Received: November 5, 2009

Tertiary amines have been demonstrated to be capable of undergoing nitrosative cleavage to produce carcinogenic *N*-nitrosamines. The reaction mechanism of the nitrosation of trimethylamine (TMA) to produce *N*-nitrosodimethylamine (NDMA) was investigated at the CBS-QB3 level of theory. The formation of NDMA from TMA was proposed to be initiated by the formation of an iminium ion, $\text{Me}_2\text{N}^+=\text{CH}_2$. Two different mechanisms (NOH elimination mechanism and oxidation abstraction mechanism) leading to $\text{Me}_2\text{N}^+=\text{CH}_2$ were investigated, and the oxidation abstraction mechanism was found to be mainly operative. This result indicates that the oxidation abstraction mechanism plays an important role in the nitrosation of both *N,N*-dialkyl aromatic and tertiary aliphatic amines. Starting from the iminium ion, two experimentally proposed mechanisms (pathways 1 and 2) and one new mechanism (pathway 3) were examined. Pathway 1 proposes that the iminium ion undergoes hydrolysis to give dimethylamine (DMA), which then can be further nitrosated to NDMA; pathway 2 proposes that the iminium ion reacts with NO_2^- and forms a neutral intermediate, which then collapses to NDMA. In pathway 3, the iminium ion reacts with N_2O_3 to give NDMA. Calculation results indicate that in aqueous solution pathway 1 is more feasible than pathways 2 and 3; moreover, the transformation from the iminium ion to NDMA is the rate-determining step. This work will be helpful to elucidate the formation mechanisms of the carcinogenic *N*-nitrosamines from the nitrosation of tertiary amines.

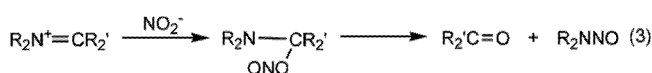
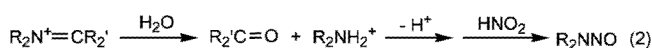
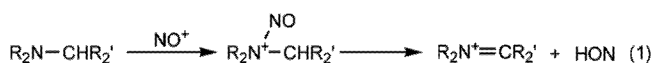
1. Introduction

It is well known that *N*-nitrosamines are a class of undesired industrial and environmental pollutants, many of which are carcinogenic, mutagenic, and teratogenic.^{1–7} In particular, *N*-nitrosodimethylamine (NDMA), which is the simplest dialkyl nitrosamine, has been demonstrated to be a potent carcinogen to various organs in animals, including liver, lung, and kidney.^{8–12} As reported, NDMA has been found in air, soil, water, food, cosmetics, rubber products, and many other materials.^{13–25} Therefore, the U.S. Environmental Protection Agency (U.S. EPA) defined NDMA as a probable human carcinogen.²⁶

Because dialkyl nitrosamines are of great interest in carcinogenesis, much attention has been focused on their formation mechanism, especially from secondary amines. Consequently, NDMA is generally believed to be formed from the reactions of dimethylamine (DMA) and nitrosating agents, such as N_2O_3 , N_2O_4 , and ONCl.^{27–31} In addition to secondary amines, however, a wide variety of tertiary amines have also been demonstrated to react with nitrous acid to produce *N*-nitrosamines in aqueous solution.^{32–44} In view of the ubiquity of tertiary amines, it is significant to understand the formation mechanism of *N*-nitrosamines from them, especially the formation of NDMA.

Previous experimental studies revealed that the nitrosation of tertiary amines proceeds via complex mechanisms depending on the structure of the amine, molar ratio of amine to nitrite, temperature, and pH.^{34,35,38,42} Different from the nitrosation of secondary amines, it has been found that a relatively weak acid solution and mild warming are generally required for the *N*-nitrosamines formation from tertiary amines.^{33,34,45} In addition, an α hydrogen atom is also required to exist in tertiary amine

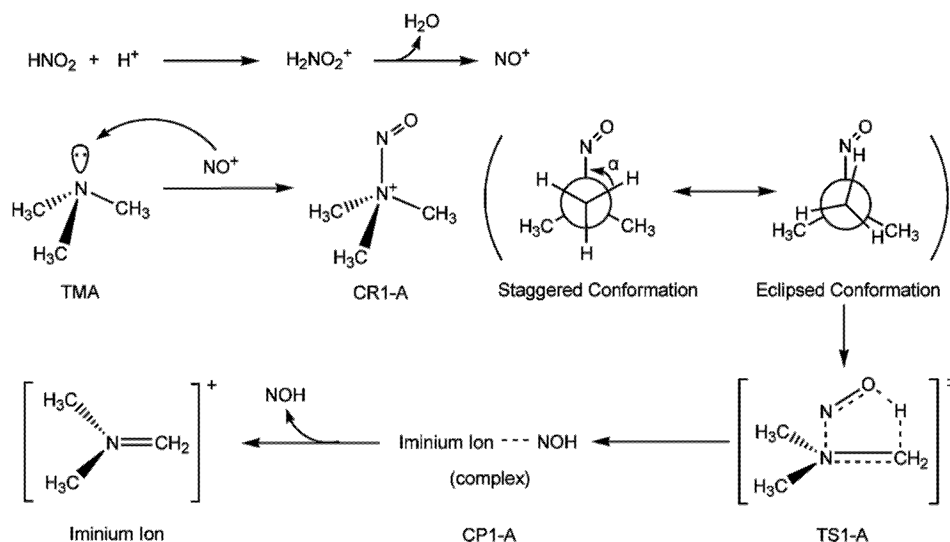
for the reaction to proceed.³³ On the basis of experimental results, the reactions were presumed to take place through the elimination of NOH from a nitrosammonium ion to produce an iminium ion $\text{R}_2\text{N}^+=\text{CR}_2'$, which then undergoes hydrolysis and further nitrosation (eqs 1 and 2). On the basis of this hypothesis, a viable alternative was then advanced as eq 3, implying the possibility of nucleophilic attack of NO_2^- toward the iminium ion to give the *N*-nitrosamine. Noticeably, the mechanisms described in eqs 1–3 became predominant in subsequent studies on the *N*-nitrosamines formation from normal aliphatic tertiary amines.



Several experimental studies of the reaction of simple aliphatic tertiary amines and nitrite obtained the similar result that the optimum pH for the production of the corresponding *N*-nitrosamines at elevated temperature (100 °C) is about 3.0 to 3.3.^{37,38,41,46} It is noteworthy that the formation of nitrosating agent N_2O_3 is facilitated at this acidity. This suggests that a new mechanism rather than the mechanisms proposed as eqs 1–3 might become operative. A kinetic study performed by Ohshima and Kawabata⁴⁶ found that the rate of NDMA formation from TMA at pH 3.0 and 100 °C is proportional to the square of nitrite concentration. Therefore, a mechanism similar to eqs 1 and 2 was proposed, where the nitrosating agent

* Corresponding author. Fax: +86-10-6739-2001. E-mail: ydliu@bjut.edu.cn.

SCHEME 1: Mechanistic Pathway for the Formation of Iminium Ion with the NOH Elimination Mechanism



was suggested to be N₂O₃ rather than HNO₂. This hypothesis is reasonable because N₂O₃ has been demonstrated to be a more potent nitrosating agent than HNO₂ in the nitrosation of secondary amines.³⁰ However, the possibility for the direct nitrosation of the iminium ion by N₂O₃ has not yet been taken into consideration.

In addition, two recent studies^{47,48} suggested that the tertiary amine may be an important precursor of carcinogenic NDMA during water disinfection process, and the proposed mechanism also involves the dealkylation of tertiary amine, which is similar to the proposed nitrosation mechanism of tertiary amines. Therefore, the investigation of the nitrosation mechanism of tertiary amines may also provide a useful model to investigate the newly found reaction, which may take place during water treatment.

Few theoretical investigations were found to make contributions to elucidate the reaction mechanism of nitrosation of tertiary amines. To better understand this kind of reaction, the present work is a theoretical research on the detailed mechanistic pathways for the formation of *N*-nitrosamine from the reaction of tertiary amine with nitrite. Trimethylamine (TMA), the simplest trialkylamine and one that can be derived from the ordinary diet,^{49–51} has been suggested to be a possible precursor of NDMA,^{38,46,52} and so it was selected as the model compound.

2. Theoretical Methods

All structures of reactants, transition states, intermediates, and products were fully optimized by using the B3LYP method (Becke's three-parameter nonlocal exchange functional⁵³ with the correlation functional of Lee, Yang, and Parr⁵⁴) in conjunction with 6-311+G(d,p) basis set. Vibrational frequencies were also calculated at the same level to characterize the nature of each stationary point. The intrinsic reaction coordinate (IRC)⁵⁵ calculations were performed to confirm that every transition state connects the corresponding reactant and product through the minimized-energy pathway. On the basis of the optimized geometries at the B3LYP/6-311+G(d,p) level, reoptimizations of these stationary points were performed with the complete basis set (CBS-QB3) methodology, in which B3LYP density functional theory is combined with the CBSB7 basis set.⁵⁶

Because the proposed mechanisms are expected to take place in aqueous solution, the solvent effect of water on the reactions of NDMA formation from TMA was also taken into account

in this study. On the basis of the optimized geometries obtained at the CBS-QB3 level, the single-point energy calculation was carried out by using the conductorlike polarizable continuum model (CPCM)⁵⁷ at the CCSD(T)/6-311+G(d,p) level,⁵⁸ denoted as CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7. According to the calculation results from Takano and Houk,⁵⁹ the UAKS cavity was used in this study to evaluate the aqueous solvation effects, and the rest of the parameters of the models have been kept as default values from the Gaussian 03 program package.⁶⁰ Because the improved density functional PBE1W has been proven to be better than B3LYP method for calculating the energies of water clusters,^{61,62} we also investigated the hydrolysis mechanism by using the PBE1W method, and the result will be used to compare with that at the CBS-QB3 level. The absolute energy data are provided in the Supporting Information. All calculations presented in this work were carried out with the Gaussian 03 program package.

3. Results and Discussion

3.1. Formation of the Iminium Ion. Two different pathways were investigated to elucidate the formation of the iminium ion. The first pathway is the mechanism described in eq 1, which involves the formation of a nitrosammonium ion Me₃NNO⁺, followed by elimination of NOH to give the iminium ion (NOH elimination mechanism). The second pathway is a new mechanism recently proposed by Loeppky et al.⁶³ This mechanism involves the oxidation of the tertiary amines to a radical cation by NO⁺, followed by the H-abstraction to produce the iminium ion by nitrogen dioxide, NO₂ (oxidation abstraction mechanism). The two mechanisms will be discussed in turn.

3.1.1. NOH Elimination Mechanism. The NOH elimination mechanism involves the formation of a nitrosammonium ion (Me₃NNO⁺) and followed by elimination of NOH to give the iminium ion. The detailed reaction pathway is illustrated in Scheme 1, and the fully optimized structures of all stationary points involved in this process are shown in Figure 1. The relative energies are listed in Table 1.

As shown in Scheme 1, TMA first undergoes electrophilic attack of NO⁺ to form a nitrosammonium ion, which is a positively charged reactant complex (CR1-A). Figure 1 shows that the N–N bond length and the angle ∠O–N–N in CR1-A were predicted to be 1.884 Å and 111.9°, respectively. As listed in Table 1, the enthalpy change (Δ*H*) was calculated to be

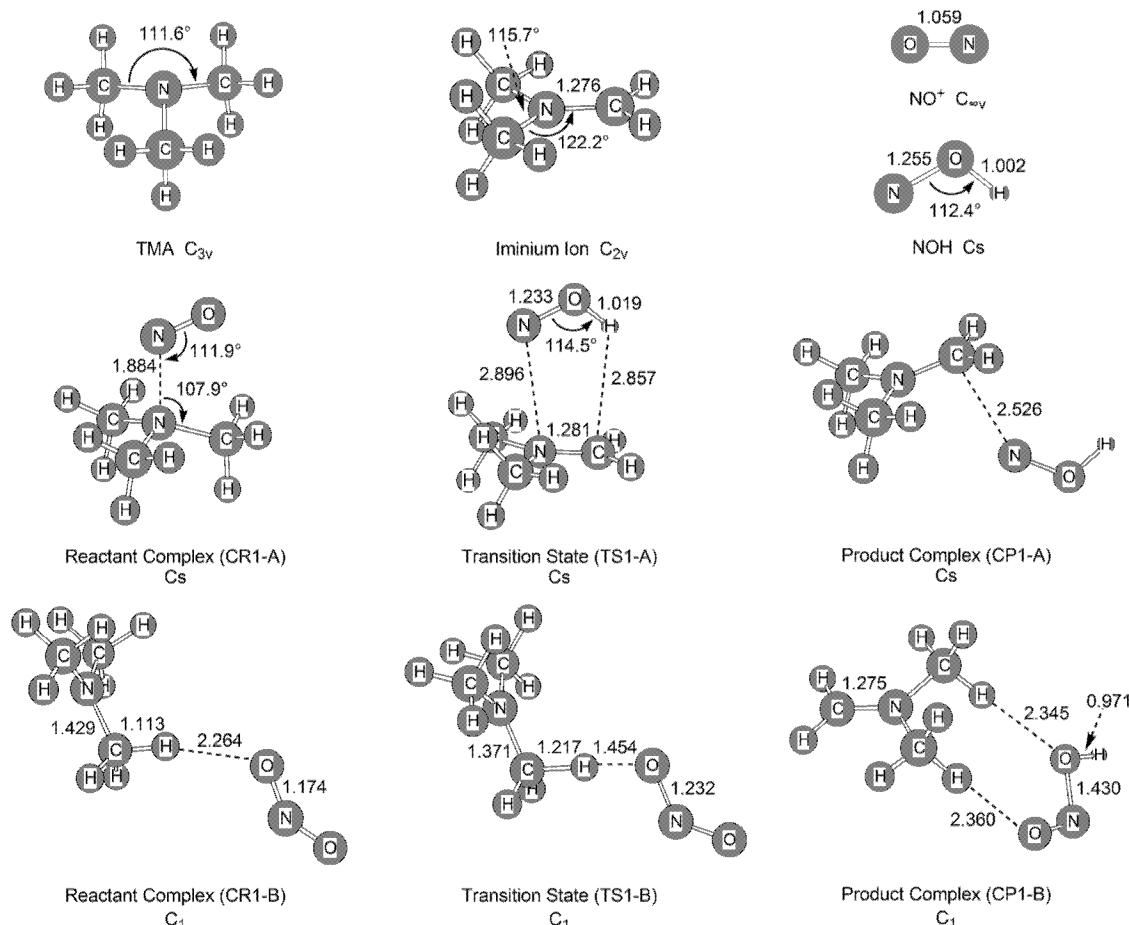


Figure 1. Optimized geometries and main parameters of all stationary points involved in the process of the formation of the iminium ion (distances in angstroms).

TABLE 1: Relative Energies (RE), Enthalpies (RH), and Free Energies (RG) of each Stationary Point Involved in the Formation of the Iminium Ion at the CBS-QB3 Level in the Gas Phase and Aqueous Solution^{a,b}

species	RE	RH	RG	RE _{aq} ^b
NOH elimination mechanism				
TMA + NO ⁺	0.00	0.00	0.00	0.00
CR1-A	-58.64	-58.97	-50.33	-20.65
TS1-A	-3.80	-3.96	3.94	32.97
CP1-A	-10.46	-10.14	-3.85	27.66
iminium ion + NOH	-2.20	-1.84	-3.64	29.88
oxidation abstraction mechanism				
TMA ⁺ + NO ₂	0.00	0.00	0.00	0.00
CR1-B	-27.71	-27.19	-20.05	48.53
TS1-B	17.26	16.78	27.32	39.02
CP1-B	-47.96	-47.98	-39.08	-46.12
iminium ion + HNO ₂	-40.83	-41.38	-39.30	-45.24

^a Gas phase: relative energies, enthalpies, and free energies in kilocalories per mole. ^b Aqueous solution: relative energies (RE_{aq}) in water at the CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7 level for comparison.

-58.97 kcal/mol, which indicates that the formation of CR1-A is an exothermic process in the gas phase. The change of Gibbs free energies (ΔG) was calculated to be -50.33 kcal/mol, indicating that the formation of CR1-A from TMA and NO⁺ is thermodynamically favored and can take place spontaneously at 298 K and 1 atm. Then, a cis elimination of NO moiety with a hydrogen atom from an α -carbon in CR1-A occurs to produce

the NOH and iminium ion. Reaction barrier for this elimination was predicted to be 54.84 kcal/mol in the gas phase.

Moreover, Scheme 1 shows that two steps are required for the formation of iminium ion. The first step is the transformation of CR1-A from a staggered conformation to an eclipsed one, which was caused by the rotation of N-C single bond. To characterize the nature of this transformation, an additional calculation of potential energy surface (PES) scan was performed at the B3LYP/CBSB7 level, and the result was illustrated in Figure 2. As shown in the PES, the energy continually increases when changing from the staggered conformation to the eclipsed one, and the energy gap between the two conformations is only 1.51 kcal/mol at the CBS-QB3 level, which indicates that the transformation occurs easily. It is interesting to note that the eclipsed conformation of CR1-A per se is not a stationary point but a transition state on the PES because the imaginary frequency is 155.2i cm⁻¹. The vibrational mode of this imaginary frequency corresponds to a rocking vibration of the methyl group through the rotation of the N-C single bond and connects two identical staggered conformations. In the second step, a five-membered cyclic transition state (TS1-A, 137.7i cm⁻¹) is formed from CR1-A in the eclipsed conformation. As illustrated in Figure 1, the N-N and H-C distances in TS1-A were calculated to be 2.896 and 2.857 Å, respectively. These unexpectedly long distances were possibly caused by the fact that the positively charged TS1-A is an electron deficient species. In addition, only slight differences were found between the geometries of NOH moiety in TS1-A and the fully optimized NOH molecule with C_s point group, as shown in Figure 1. A

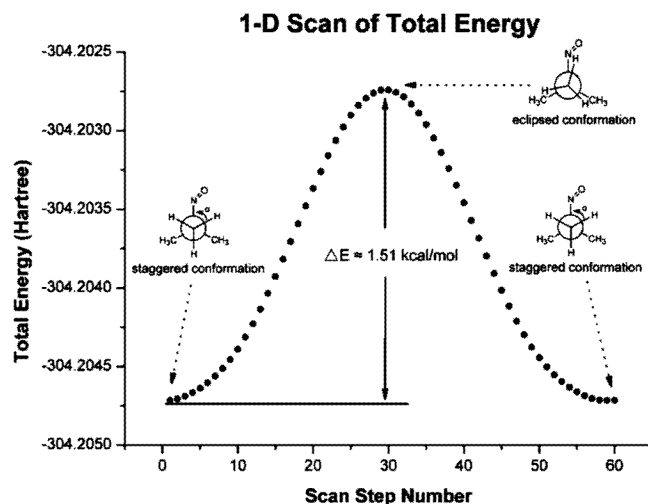
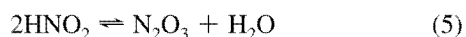
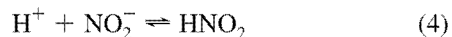


Figure 2. Scan plot of potential energy surface (PES) for the transformation of CR1-A from the staggered conformation to the eclipsed conformation at the B3LYP/CBSB7 level.

similar situation can also be observed between the other moiety of TS1-A and the fully optimized iminium ion. Both of the vibrational mode of imaginary frequency and IRC calculations at the B3LYP/6-311+G(d,p) level confirm that this transition state does connect the corresponding reactant complex (CR1-A) and product complex (CP1-A). The energy required to separate the NOH and iminium ion from CP1-A was calculated to be 8.26 kcal/mol, as shown in Table 1.

3.1.2. Oxidation Abstraction Mechanism. The oxidation abstraction mechanism involves the oxidation of the TMA to a radical cation by NO^+ and then followed by the H-abstraction to produce the iminium ion by NO_2 . The detailed reaction pathway of this mechanism is illustrated in Scheme 2, and the fully optimized structures of all stationary points involved in this mechanism are shown in Figure 1. The relative energies are listed in Table 1.

As shown in Scheme 2, similar as the case of Scheme 1, TMA first undergoes electrophilic attack of NO^+ to form the nitrosammonium ion (CR1-A). This is followed by the elimination of nitric oxide NO to produce a radical cation, TMA^+ . The TMA^+ further undergoes the H-abstraction by the attack of NO_2 to form the iminium ion and HNO_2 . The origin of the radical NO_2 is described as eqs 4–6. Two HNO_2 molecules first react to yield N_2O_3 , followed by the homolytic dissociation of the N–N bond in N_2O_3 to give NO_2 .



The total energy of the TMA^+ and NO was calculated to be remarkably lower than that of the TMA and NO^+ by 33.51 kcal/mol. This result implies that the oxidation of TMA to TMA^+ by NO^+ is exothermic. It is illustrated in Figure 1 that the main geometrical change for the reaction of TMA^+ and NO_2 is the transfer of a hydrogen atom from the TMA^+ to NO_2 . It is noteworthy that the energy barrier of the oxidation abstraction mechanism in the gas phase was calculated to be 44.97 kcal/mol, which is lower than the barrier of the NOH elimination mechanism (54.84 kcal/mol), as shown in Table 1.

It should be noted that both the NOH elimination and oxidation abstraction mechanisms proposed the positively

charged NO^+ as the oxidative species in this article. However, there is still the possibility of the other species such as NO_2 or N_2O_3 as the oxidant. Therefore, what is the oxidative species to amines may be still an open question.

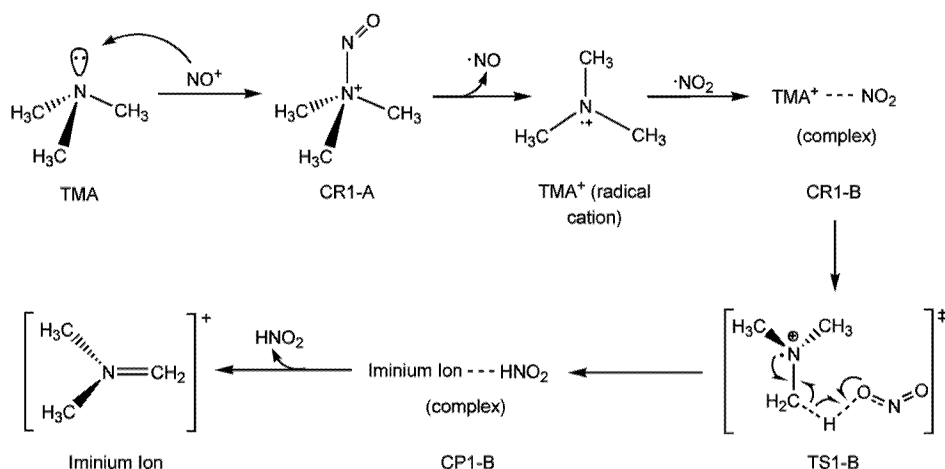
3.2. Formation of NDMA from Iminium Ion. Generally, there are two main reaction mechanisms for the formation of NDMA from the iminium ion. In the first mechanism, the iminium ion undergoes hydrolysis to be degraded to a secondary amine DMA, which can then be further nitrosated to NDMA. In the second mechanism, the iminium ion directly reacts with nitrosating species (NO_2^- or N_2O_3) to produce NDMA. In this study, three pathways were considered. Pathway 1 belongs to the first mechanism, in which the iminium ion undergoes hydrolysis to form DMA. Pathways 2 and 3 belong to the second mechanism, in which the iminium ion undergoes a nucleophilic attack from NO_2^- and N_2O_3 , respectively, and then collapses to NDMA. The former two pathways were proposed on the basis of previous experimental results, and the third is a pathway that was put forward on the basis of the fact that N_2O_3 can be formed under the mild acid condition. Detailed discussions for pathways 1, 2, and 3 will be given in turn.

3.2.1. Reaction Pathway 1: Hydrolysis Mechanism. Pathway 1 proposes that the nascent iminium ion undergoes hydrolysis to give a protonated adduct, which then loses a H^+ to give a formaldehyde molecule and DMA, which will be nitrosated finally to NDMA. Two different hydrolysis mechanisms were examined: (A) non-assisted hydrolysis mechanism (only one H_2O molecule involved) and (B) water-assisted hydrolysis mechanism (two H_2O molecules involved). Because the improved density functional PBE1W has been proven to be better than the B3LYP method for calculating the energies of water clusters,^{60,61} the hydrolysis mechanism was also investigated by using the PBE1W method, and the result will be used to compare with that at the CBS-QB3 level (Tables 2 and 3). The detailed reaction pathways are illustrated in Schemes 3 and 4. The hybridization change of N and C atoms involved in the mechanism is described in Figure 3, and the fully optimized structures of all stationary points involved in this mechanism are shown in Figures 4 and 5. The relative energies are listed in Tables 2 and 3.

A. Non-Assisted Hydrolysis Mechanism. As illustrated in Scheme 3, a reactant complex (CR2-A) composed of the nascent iminium ion and one H_2O molecule is first formed. Table 2 shows that the enthalpy change ΔH for the formation of CR2-A was calculated as -9.21 kcal/mol, which predicts an exothermic process. As illustrated in Figure 3, in CR2-A, the N and C atoms are sp^2 hybridized, and the p orbitals of the N and C atoms that are perpendicular to the planar iminium ion overlap each other and form a stable conjugated system. The iminium ion moiety shows a planar structure in which the dihedral angles $D(\text{C}-\text{N}-\text{C}-\text{C})$ and $D(\text{H}-\text{C}-\text{H}-\text{N})$ are 178.5 and 178.7° (Figure 4), respectively.

Further approach of the iminium ion and H_2O leads to the formation of a four-membered cyclic transition state (TS2-A, 1374.1i cm^{-1}). In this process, as shown in Figure 4, the O–C bond length decreases from 2.549 to 1.513 Å, whereas the distance between H and N atoms reduces from 3.786 to 1.478 Å, which indicates the formation of C–O and N–H bonds. H–O and N–C bond lengths are increased by 0.182 and 0.177 Å, respectively, which indicates the cleavage of these two bonds. The dihedral angles of $D(\text{C}-\text{N}-\text{C}-\text{C})$ and $D(\text{H}-\text{C}-\text{H}-\text{N})$ reduce to 134.8 and 135.2° when changing from CR2-A to TS2-A, respectively, which implies that the original sp^2 hybridized N and C atoms in CR2-A are going to convert to sp^3

SCHEME 2: Mechanistic Pathway for the Formation of Iminium Ion with the Oxidation Abstraction Mechanism

TABLE 2: Relative Energies (RE), Enthalpies (RH), and Free Energies (RG) of Each Stationary Point Involved in the Non-Assisted Hydrolysis Mechanism at the CBS-QB3 Level in the Gas Phase and Aqueous Solution^{a,b,c}

species	RE	RH	RG	RE _w ^b	RE _w ^c
iminium ion + H ₂ O	0.00	0.00	0.00	0.00	0.00
CR2-A	-9.33	-9.21	-3.01	-3.21	-3.24
TS2-A	30.88	29.20	40.34	29.63	29.39
CP2-A	-6.99	-8.24	1.68	-14.42	-16.28

^a Gas phase: relative energies, enthalpies, and free energies in kilocalories per mole. ^b Aqueous solution: relative energies (RE_w) in water at the CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7 level for comparison. ^c Aqueous solution: relative energies (RE_w) in water at the CPCM-CCSD(T)/6-311+G(d,p)//PBE1W/CBSB7 level for comparison.

TABLE 3: Relative Energies (RE), Enthalpies (RH), and Free Energies (RG) of Each Stationary Point Involved in the Water-Assisted Hydrolysis Mechanism at the CBS-QB3 Level in the Gas Phase and Aqueous Solution^{a,b,c}

species	RE	RH	RG	RE _w ^b	RE _w ^c
iminium ion + 2H ₂ O	0.00	0.00	0.00	0.00	0.00
CR2-B	-17.44	-18.22	-1.87	-6.83	-5.16
TS2-B	5.97	3.31	24.64	8.47	8.24
CP2-B	-21.90	-23.52	-4.86	-19.36	-19.18

^a Gas phase: relative energies, enthalpies, and free energies in kilocalories per mole. ^b Aqueous solution: relative energies (RE_w) in water at the CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7 level for comparison. ^c Aqueous solution: relative energies (RE_w) in water at the CPCM-CCSD(T)/6-311+G(d,p)//PBE1W/CBSB7 level for comparison.

hybridization in the process, as illustrated in Figure 3. The conversion of hybridization makes the N and C atoms more capable of accepting the H and O atoms of the H₂O molecule, respectively. In fact, the hybridization of N and C atoms in TS2-A is more like a middle state between sp² and sp³, and further decreased *D*(C–N–C–C) and *D*(H–C–H–N) can be observed in the product complex (CP2-A) when compared with that of TS2-A (Figure 4).

As shown in Table 2, the energy barrier for this reaction was calculated to be 40.21 kcal/mol in the gas phase. This relatively high barrier can be rationalized by the stable CR2-A and the high-lying four-membered cyclic transition state TS2-A with strong ring strain.

Natural bond orbital (NBO) analysis⁶⁴ for CP2-A showed that the highest positively charged position locates at the hydrogen atom H (+0.500 e) adjacent to oxygen atom. Therefore, this

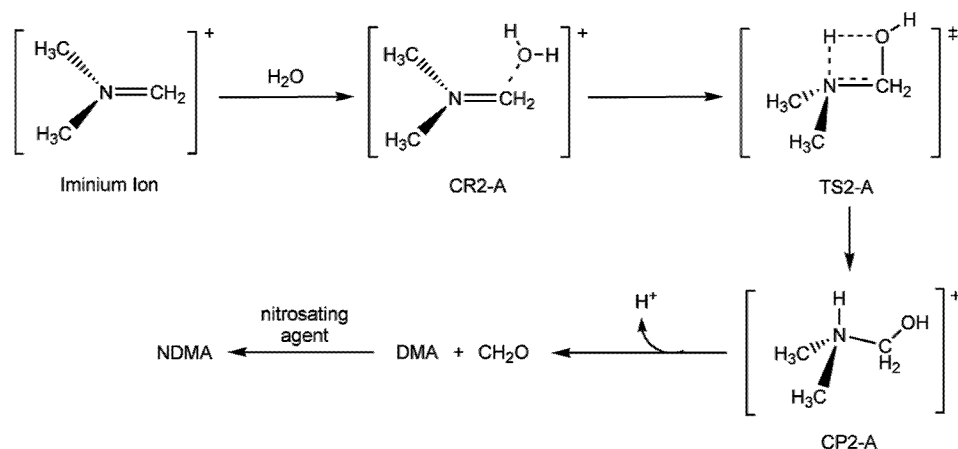
hydrogen atom might be expected to easily undergo the attack of nucleophiles in solution. Consequently, the loss of a proton H⁺ will give rise to the formaldehyde and DMA, which can be further nitrosated to NDMA by a nitrosating agent, as shown in Scheme 3.

B. Water-Assisted Hydrolysis Mechanism. Two H₂O molecules are required for the water-assisted hydrolysis mechanism in Scheme 4, which is different from the non-assisted hydrolysis mechanism. It is shown that a reactant complex (CR2-B) between the nascent iminium ion and two H₂O molecules is first formed. As shown in Table 3, enthalpy change ΔH for the formation of CR2-B was calculated to be -18.22 kcal/mol, which predicts that this formation is an exothermic process in the gas phase. Similar to the case of CR2-A, in Figure 5, the N and C atoms in CR2-B are sp² hybridized because the iminium ion moiety shows a planar structure in which the dihedral angles *D*(C–N–C–C) and *D*(H–C–H–N) are 173.7° and 174.1°, respectively. As discussed in the non-assisted hydrolysis mechanism, the planar structure indicates the formation of an intramolecular stable conjugated system.

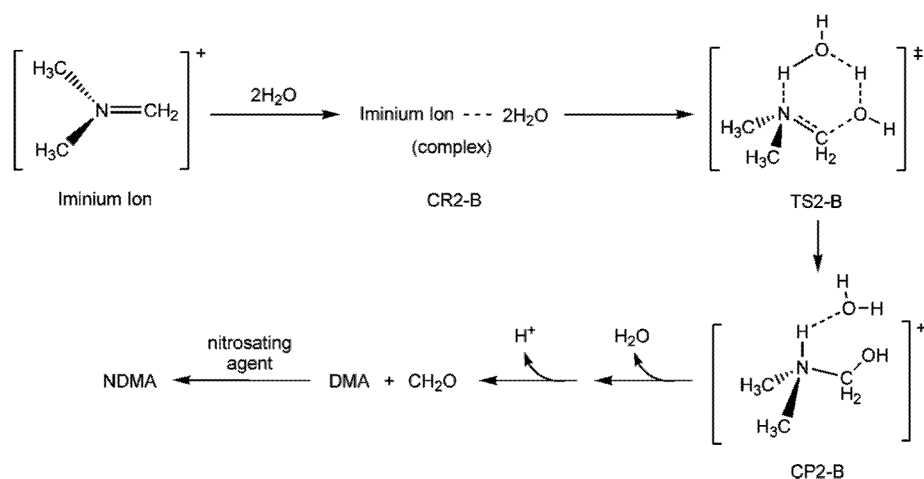
As shown in Scheme 4, further approach of the iminium ion and H₂O molecules in CR2-B leads to the formation of a six-membered cyclic transition state (TS2-B, 276.5i cm⁻¹). In this process, the O–C bond length decreases from 2.372 to 1.503 Å, whereas the N–C bond length increases from 1.281 to 1.427 Å. The dihedral angles of *D*(C–N–C–C) and *D*(H–C–H–N) reduce to 128.5 and 129.8° when changing from CR2-B to TS2-B, respectively, which implies that the original sp² hybridized N and C atoms in CR2-B are going to convert to sp³ hybridization in the process, as illustrated in Figure 5. Further changes following these tendencies give rise to the product complex (CP2-B), in which the O–C bond length decreases to 1.384 Å, whereas the N–C bond length increases to 1.525 Å, and the dihedral angles of *D*(C–N–C–C) and *D*(H–C–H–N) reduce to 127.4 and 115.8°, respectively. Similar to the case of Scheme 3, Scheme 4 shows that the loss of a water molecule and a proton H⁺ from the nascent CP2-B gives the formaldehyde and DMA, which can be further nitrosated to NDMA by a nitrosating agent. The nitrosation of secondary amines has already been extensively studied,^{27–31} and the DMA has been confirmed to be easily nitrosated into NDMA in an acidic nitrite solution.

As shown in Table 3, the energy barrier for water-assisted hydrolysis mechanism was calculated to be 23.41 kcal/mol in the gas phase. It is notable that this barrier is almost half the magnitude of the barrier for the non-assisted hydrolysis mech-

SCHEME 3: Mechanistic Pathway for the Formation of NDMA with the Non-Assisted Hydrolysis Mechanism of Pathway 1



SCHEME 4: Mechanistic Pathway for the Formation of NDMA with the Water-Assisted Hydrolysis Mechanism of Pathway 1



anism (40.21 kcal/mol). This lower energy barrier can be rationalized by the fact that the transition state TS2-B, composed of a six-membered ring, is much more stable than the high-lying four-membered cyclic transition state TS2-A.

In addition to the hydrolysis mechanisms discussed above, the oxygen atom of water molecule may also attack the iminium ion to the nitrogen atom to form two different transition states (TS2-A' and TS2-B'). These possibilities were also examined; however, the corresponding energy barriers were predicted to be high as 77.78 and 62.93 kcal/mol at the PBE1W/CBSB7 level in the gas phase, respectively. Therefore, they are not expected to occur. The absolute energies were collected in the Supporting Information (Tables S13 and S14).

3.2.2. Reaction Pathway 2: Nucleophilic Attack of NO_2^- .

The iminium ion, which is known to be highly reactive toward nucleophiles,^{65,66} could therefore be expected to easily undergo the nucleophilic attack by free nitrite (NO_2^-) to give a neutral prereactant (designated as PR3). This prereactant then directly collapses to formaldehyde and NDMA. The detailed reaction pathway is illustrated in Scheme 5, and the fully optimized structures of all stationary points involved in this pathway are collected in Figure 6. The relative energies are listed in Table 4.

As shown in Scheme 5, after the formation of PR3, the movement of electrons may occur to give a transition state (TS3, 383.5i cm^{-1}). It can be found that TS3 is not a real four-

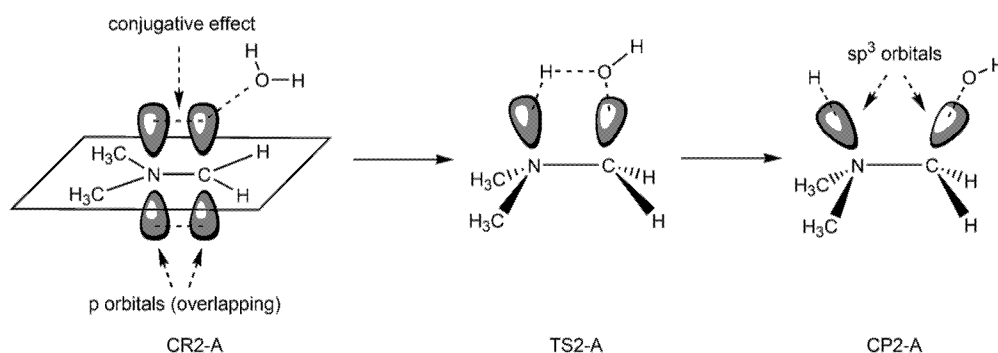


Figure 3. Schematic profile for the conversion of hybridization of N and C atoms involved in the non-assisted hydrolysis mechanism of pathway 1.

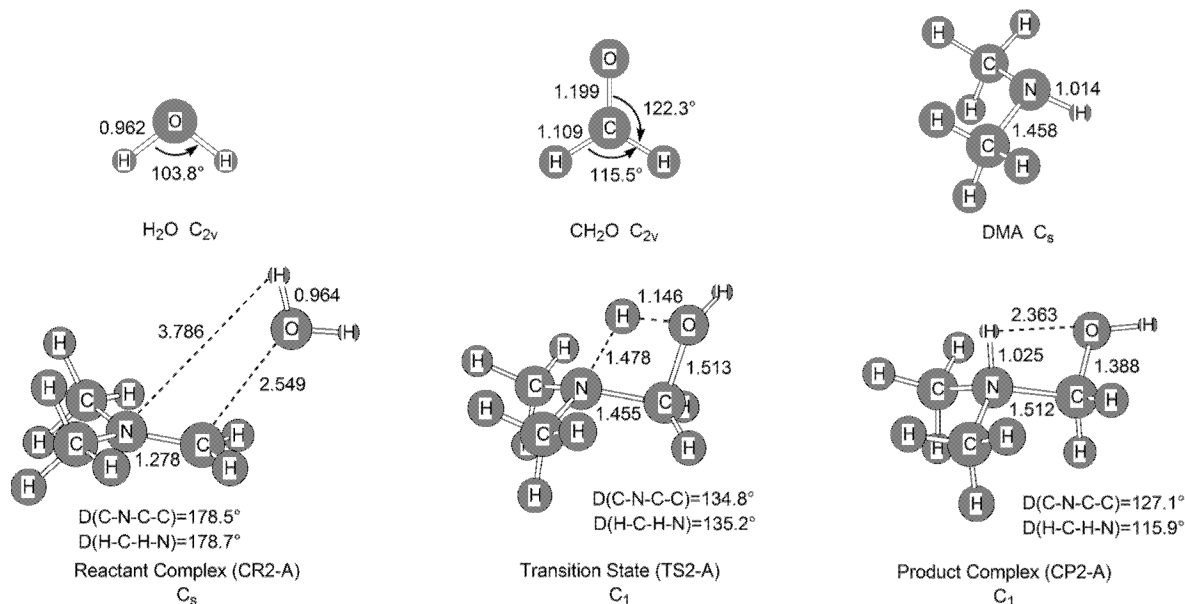


Figure 4. Optimized geometries and main parameters of all the stationary points involved in the non-assisted hydrolysis mechanism of pathway 1 (distances in angstroms, dihedral angle in degrees).

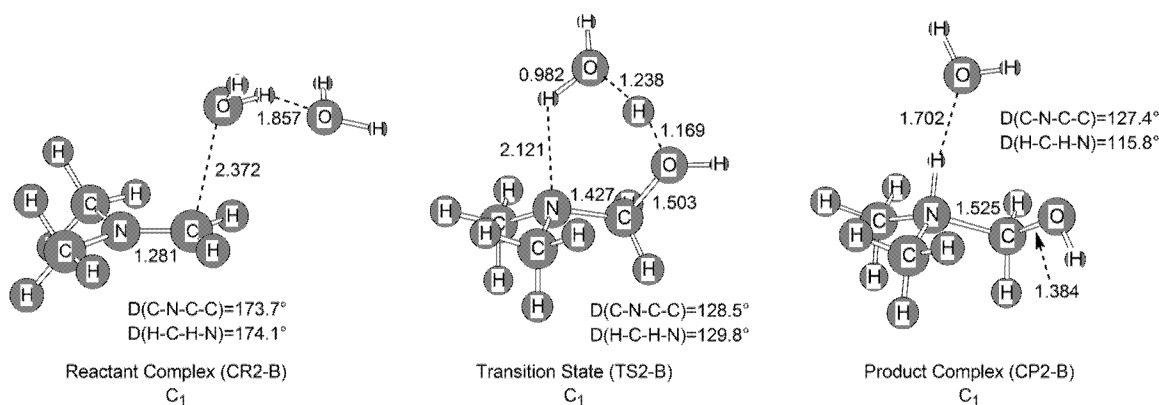
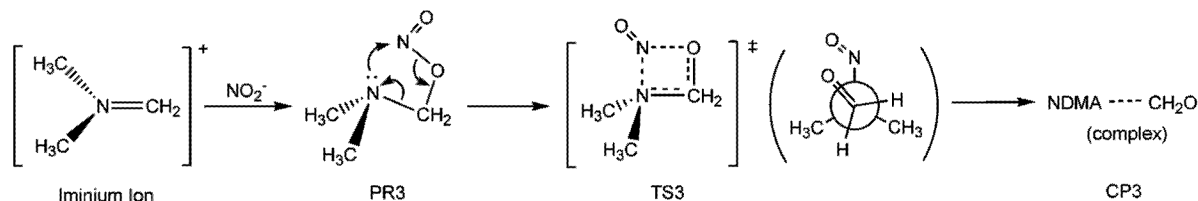


Figure 5. Optimized geometries and main parameters of all the stationary points involved in the water-assisted hydrolysis mechanism of pathway 1 (distances in angstroms, dihedral angle in degrees).

SCHEME 5: Mechanistic Pathway for the Formation of NDMA in Pathway 2



membered cyclic transition state. Newman projection in Scheme 5 implies that TS3 actually holds a conformation between the staggered and eclipsed one, and this is supported by the dihedral angle *D*(O-C-N-N) calculated to be 45.3°. (See Figure 6.) It can be rationalized by the fact that this conformation avoids strong ring strain and steric hindrance for stabilization. In the process from PR3 to TS3, the changes of bonds shown in Figure 6 indicate that the original N-C and N-O bonds are partially cleaved, whereas the N-N bond is partially formed. The C-O bond length decreases from 1.430 to 1.257 Å, indicating that a double bond is formed. As shown in Table 4, in the gas phase, the energy barrier for the reaction was calculated to be 27.94 kcal/mol, which is close to that of the water-assisted hydrolysis mechanism in pathway 1 (23.41 kcal/mol).

In the process from TS3 to CP3, two types of geometric changes can be observed: the elongation of the distances of N-C

and N-O bonds between CH₂O moiety and the other and the reduction of N-N and C-O bond lengths. In addition, the changes of the two moieties from their previous tetrahedral configuration to a planar configuration demonstrate that both of the N and C atoms change from sp³ to sp² hybridization. Furthermore, changes of the geometry will form the product complex (CP3), in which the formaldehyde and NDMA are connected by two O-H hydrogen bonds, as shown in Figure 6.

3.2.3. Reaction Pathway 3: Direct Nitrosation by N₂O₃. As discussed previously, the optimum pH for the conversion of TMA to NDMA at elevated temperature has been proven experimentally to be about 3.0 to 3.3.^{37,38,41,46} It is well known that within this pH range N₂O₃ can be easily formed. On the basis of these results, a new mechanism is proposed in which the iminium ion directly reacts with N₂O₃. The detailed reaction

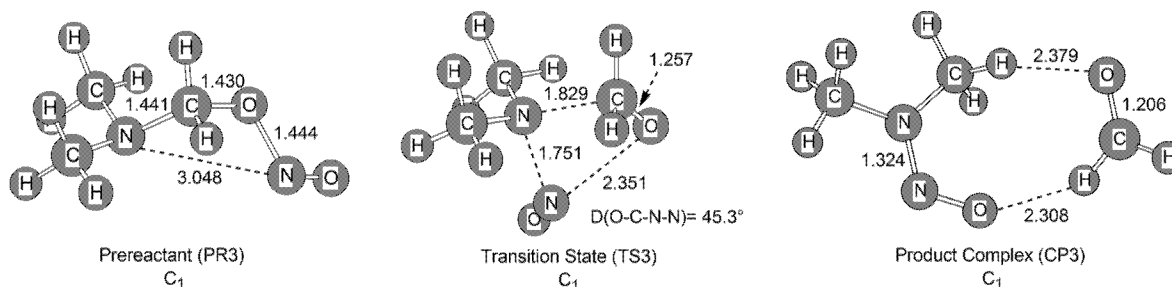


Figure 6. Optimized geometries and main parameters of all stationary points involved in pathway 2 (distances in angstroms, dihedral angle in degrees).

TABLE 4: Relative Energies (RE), Enthalpies (RH), and Free Energies (RG) of Each Stationary Point Involved in the Reaction of the Iminium Ion with NO_2^- at the CBS-QB3 Level in the Gas Phase and Aqueous Solution^{a,b}

species	RE	RH	RG	RE _w ^b
iminium ion + NO_2^-	0.00	0.00	0.00	0.00
PR3	-128.18	-128.74	-117.58	-15.21
TS3	-100.24	-100.72	-89.27	10.25
CP3	-133.31	-132.58	-125.33	-18.95
CH_2O + NDMA	-129.67	-129.13	-130.45	-17.31

^a Gas phase: relative energies, enthalpies, and free energies in kilocalories per mole. ^b Aqueous solution: relative energies (RE_w) in water at the CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7 level for comparison.

pathway is illustrated in Scheme 6, and the fully optimized structures of all stationary points involved in this pathway are collected in Figure 7. The relative energies are listed in Table 5.

As shown in Scheme 6, two steps are required for this reaction. The first step is the nucleophilic attack of N_2O_3 to the iminium ion to produce a positively charged intermediate (IM), and the second step is the collapse of IM to give the final products: NDMA, formaldehyde, and NO^+ . It is evident that NO^+ actually plays the role of catalyst in the whole reaction, and it may reparticipate in the formation of iminium ion. (See Scheme 1.)

The nucleophilic attack of N_2O_3 to the iminium ion starts from a reactant complex CR4, followed by the formation of a five-membered cyclic transition state TS4-1 ($345.5i \text{ cm}^{-1}$), which then further produces an intermediate IM. The energy barrier of this step was calculated to be 29.12 kcal/mol in the gas phase, and the enthalpy change ΔH shown in Table 5 indicates that the reaction is an exothermic process. IRC calculation along the reverse reaction pathway shows two types of geometric changes: the elongation of O-C and N-N bond lengths between the iminium ion and N_2O_3 moieties and the reduction of N-N bond length to be N_2O_3 and C-N bond length in iminium ion moiety. These geometric changes indicate that the energy 29.12 kcal/mol required for the transformation from CR4 to TS4-1 is mainly utilized to rotate and dissociate the N-N bond in N_2O_3 as well as elongate the C-N bond in the moiety of iminium ion. During this process, the dihedral angles $D(\text{H}-\text{C}-\text{N}-\text{H})$ and $D(\text{C}-\text{N}-\text{C}-\text{C})$ reduce by 40.8 and 31.9°, respectively. This indicates that the hybridization of the N and C atoms in the iminium ion moiety change from sp^2 to sp^3 , which is similar to the case of hydrolysis mechanism (pathway 1, Figure 3). Further changes of the structure encounter an intermediate IM. It can be observed that the N-N bond in the original N_2O_3 moiety is totally separated in IM, and the original planar iminium ion moiety changes into a tetrahedron config-

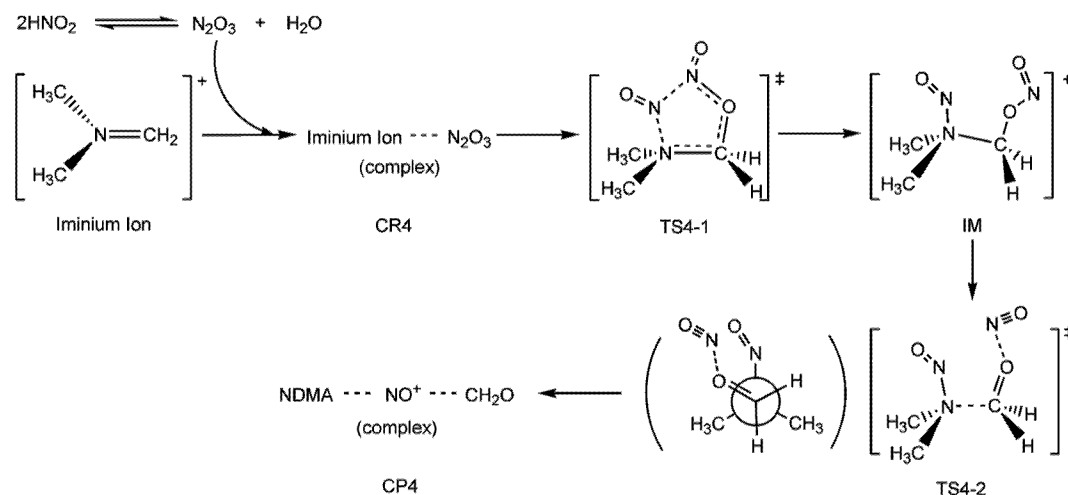
uration as a result of the further reduction of corresponding dihedral angles.

In the second step of the reaction, TS4-2 ($211.9i \text{ cm}^{-1}$) connects the nascent intermediate IM and the product complex CP4, as depicted in Scheme 6. The reaction barrier for this step was calculated as 15.31 kcal/mol, which is lower than the barrier (29.12 kcal/mol) of the first step reaction in the gas phase. This implies that the formation of the intermediate IM is the rate-determining step for pathway 3. Notably, the energy barrier (29.12 kcal/mol) of the first step is close to the barrier (23.41 kcal/mol) calculated for the water-assisted hydrolysis mechanism in pathway 1 and the barrier (27.94 kcal/mol) for pathway 2. In addition, it can be found that the products NDMA and formaldehyde have already formed in TS4-2, for which a staggered conformation can be observed. (See the Newman projection in Scheme 6.) The main vibrational mode for the imaginary frequency of TS4-2 corresponds to the stretching vibration of N-C bond, indicating that the energy requirement (15.31 kcal/mol) for overcoming the barrier is mainly utilized to dissociate the N-C bond. Additionally, N-O bond length was also found to be elongated from 1.638 to 1.895 Å when changing from IM to TS4-2. Also, the N-N and C-O bond lengths are decreased by 0.454 and 0.127 Å, respectively, predicting the formation of the two bonds. Further changes of the structure give rise to the product complex (CP4) composed of NDMA, formaldehyde, and NO^+ . It is interesting to note that the changes of hybridization of the N and C atoms exhibit a reverse process relative to that of the first step in the reaction (formation of IM from CR4), for both of the two atoms changing back to sp^2 from sp^3 hybridization. This finding is supported by the changes of the corresponding dihedral angles shown in Figure 7.

3.3. Effects of Solvent. Because the attention of this article is focused on environmental nitrosamine formation, for which most reactions should be expected to occur in aqueous solution, the solvent effect of water on NDMA formation from TMA was taken into account. On the basis of the optimized geometries obtained at the CBS-QB3 level, the single-point energy calculation was carried out by the use of the conductorlike polarizable continuum model (CPCM) at the CCSD(T)/6-311+G(d,p) level, denoted as CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7. The corresponding relative energy data (RE_w) in water are presented in Tables 1–5 for comparison with those in the gas phase.

As for the formation of the iminium ion, data in Table 1 show that the energy barrier for the NOH elimination mechanism is 53.62 kcal/mol in aqueous solution. Significantly, the oxidation abstraction mechanism becomes a barrierless process with a negative energy barrier (−9.51 kcal/mol). Moreover, the oxidation abstraction mechanism is exothermic, and a considerable energy (45.24 kcal/mol) was predicted to be released from the

SCHEME 6: Mechanistic Pathway for the Formation of NDMA in Pathway 3



reaction. Therefore, the TMA^+ would be expected to react easily with NO_2 because of the low energy barrier. The results actually lead to a conclusion that the oxidation abstraction mechanism is more favored than the NOH elimination mechanism and is probably the one that is mainly operative to form iminium ion. Noticeably, this result supports the feasibility of the experi-

mentally proposed oxidation abstraction mechanism.⁶³ Moreover, it also indicates that the newly proposed oxidation abstraction mechanism plays an important role not only in the nitrosation of *N,N*-dialkyl aromatic amines⁶³ but also in the case of tertiary aliphatic amines. Furthermore, because the formation of N_2O_3 and its cleavage product NO_2 (eqs 4–6) is facilitated

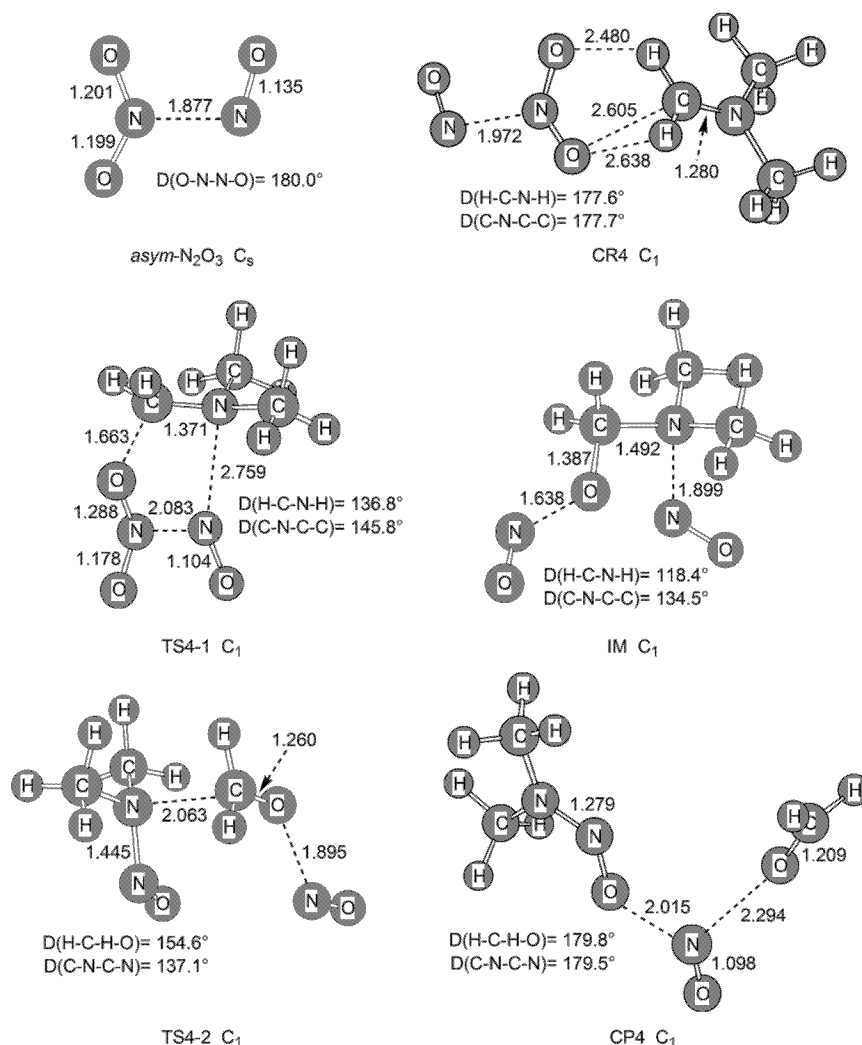


Figure 7. Optimized geometries and main parameters of all stationary points involved in pathway 3 (distances in angstroms, dihedral angle in degrees).

TABLE 5: Relative Energies (RE), Enthalpies (RH), and Free Energies (RG) of each Stationary Point Involved in the Reaction of the Iminium Ion with N₂O₃ at the CBS-QB3 level in the Gas Phase and Aqueous Solution^{a,b}

species	RE	RH	RG	RE _w ^b
iminium ion + N ₂ O ₃	0.00	0.00	0.00	0.00
CR4	-10.70	-9.97	-2.43	-1.84
TS4-1	18.42	18.16	29.55	15.12
IM	-10.92	-10.89	0.26	-10.57
TS4-2	4.39	4.30	15.87	9.55
CP4	-14.26	-13.21	-5.81	-4.68
CH ₂ O + NDMA + NO ⁺	40.76	42.12	31.13	0.59

^a Gas phase: relative energies, enthalpies, and free energies in kilocalories per mole. ^b Aqueous solution: relative energies (RE_w) in water at the CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7 level for comparison.

in pH 3.0 to 3.3, the results may also explain the experimental fact that the optimum acidity for the nitrosation of TMA within this pH range.^{37,38,41,46}

In aqueous solution, the energy barriers for the non-assisted and water-assisted hydrolysis mechanism in pathway 1 were calculated to be 32.84 and 15.30 kcal/mol, respectively, as shown in Tables 2 and 3. The energy barriers obtained at the CPCM-CCSD(T)/6-311+G(d,p)//PBE1W/CBSB7 level are 32.63 and 13.40 kcal/mol, which are close to the data at the CPCM-CCSD(T)/6-311+G(d,p)//B3LYP/CBSB7 level. This indicates that the water-assisted hydrolysis mechanism is still more favored, which is consistent with the case in the gas phase. Accordingly, a conclusion can be drawn that the water-assisted hydrolysis mechanism is more favored than the non-assisted hydrolysis mechanism and should be the one that is mainly operative. The energy barrier for the transformation from PR3 to CP3 in pathway 2 was calculated to be 25.46 kcal/mol (Table 4). With regard to pathway 3, reaction barriers for the first step reaction (formation of the intermediate IM) and the second step reaction (formation of CP4) were calculated to be 16.96 and 20.12 kcal/mol, respectively. This implies that, under experimental conditions, pathway 1 is more feasible than pathways 2 and 3 for the transformation from the iminium ion to NDMA in aqueous solution. Although the new mechanism described in pathway 3, a stepwise reaction of the iminium ion with N₂O₃, has a relatively higher energy barrier than pathway 1, it is still more favored than pathway 2, a direct reaction of the iminium ion with NO₂⁻ to form NDMA. Comparing the energy barriers of all steps in the reaction, a conclusion can be drawn that the rate-determining step in aqueous solution is the transformation from the iminium ion to NDMA.

4. Conclusions

The formation mechanisms of NDMA from the nitrosation of TMA were investigated at the CBS-QB3 level of theory. The reaction was proposed to be initiated by the formation of a highly reactive iminium ion, Me₂N⁺=CH₂. Two different pathways, that is, oxidation abstraction and NOH elimination mechanisms, were investigated to elucidate the formation of the iminium ion, and the oxidation abstraction mechanism was found to be more favored than the NOH elimination mechanism. The results not only support the feasibility of the experimentally proposed oxidation abstraction mechanism but also extend this mechanism from the nitrosation of *N,N*-dialkyl aromatic amines⁶³ into the case of tertiary aliphatic amines.

Starting from the iminium ion, three different pathways leading to NDMA were examined. Pathway 1 proposes that the

iminium ion undergoes hydrolysis to give a secondary amine DMA, which then can be directly nitrosated to NDMA. Two different hydrolysis mechanisms were examined for this pathway: non-assisted and water-assisted hydrolysis mechanisms. The energy barrier for the water-assisted hydrolysis mechanism was predicted to be almost half the magnitude of the barrier for the non-assisted mechanism, indicating that the former should be predominant. In pathways 2 and 3, the iminium ion reacts with NO₂⁻ and N₂O₃ to form a neutral and a positively charged intermediate, respectively, which then both collapse to NDMA. Comparing the three pathways in aqueous solution, pathway 1 is the most favored, and pathway 3 has a relatively lower energy barrier than pathway 2. All calculation results indicate that the rate-determining step of the whole reaction in aqueous solution is the transformation from the iminium ion to form NDMA.

On the basis of the theoretical study reported in this article, some experimental results on the *N*-nitrosamines formation from tertiary amine can be explained. This work will be helpful to elucidate the formation mechanisms of *N*-nitrosamines from tertiary amines.

Acknowledgment. We thank Mary York P. Eng. Beijing University of Technology for English language suggestion. This work was supported by National Natural Science Foundation of China (no. 20903006), Beijing Natural Science Foundation (no. 2092008) and Beijing Nova Program (no. 2008B09).

Supporting Information Available: Absolute energy for each stationary point involved in the formation of NDMA from the nitrosation of trimethylamine. These materials are available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (1) Anderson, L. M.; Souliotis, V. L.; Chhabra, S. K.; Moskal, T. J.; Harbaugh, S. D.; Kyrtopoulos, S. A. *Int. J. Cancer* **1996**, *66*, 130.
- (2) Hecht, S. S. *Chem. Res. Toxicol.* **1998**, *11*, 559.
- (3) Goto, Y.; Matsuda, T.; Ito, K.; Huh, H. H.; Thomale, J.; Rajewsky, M. F.; Hayatsu, H.; Negishi, T. *Mutat. Res.* **1999**, *425*, 125.
- (4) Lin, H. L.; Hollenberg, P. F. *Chem. Res. Toxicol.* **2001**, *14*, 562.
- (5) Wolf, T.; Niehaus-Rolf, C.; Luepke, N. P. *Food Chem. Toxicol.* **2003**, *41*, 561.
- (6) Dennehy, M. K.; Loeppky, R. N. *Chem. Res. Toxicol.* **2005**, *18*, 556.
- (7) Mittal, G.; Brar, A. P. S.; Soni, G. *Exp. Toxicol. Pathol.* **2008**, *59*, 409.
- (8) Magee, P. N.; Hultin, T. *Biochem. J.* **1962**, *83*, 106.
- (9) Tanaka, A.; Hisanaga, A.; Inamasu, T.; Hirata, M.; Ishinishi, N. *Food Chem. Toxicol.* **1988**, *26*, 847.
- (10) Anderson, L. M.; Carter, J. P.; Logsdon, D. L.; Driver, C. L.; Kovatch, R. M. *Carcinogenesis* **1992**, *13*, 2107.
- (11) Mizgireuv, I. V.; Majorova, I. G.; Gorodinskaya, V. M.; Khudoley, V. V.; Revskoy, S. Y. *Toxicol. Pathol.* **2004**, *32*, 514.
- (12) Fukushima, S.; Wanibuchi, H.; Morimura, K.; Nakae, D.; Tsuda, H.; Imaida, K.; Shirai, T.; Tatematsu, M.; Tsukamoto, T.; Hirose, M.; Furukawa, F. *Cancer Lett.* **2005**, *222*, 11.
- (13) Oliver, J. E. *J. Environ. Qual.* **1979**, *8*, 596.
- (14) Sen, N. P.; Seaman, S.; Miles, W. F. *J. Agric. Food. Chem.* **1979**, *27*, 1354.
- (15) Stehlik, G.; Richter, O.; Altmann, H. *Ecotoxicol. Environ. Saf.* **1982**, *6*, 495.
- (16) Spiegelhalter, B.; Preussmann, R. *J. Cancer Res. Clin. Oncol.* **1984**, *108*, 160.
- (17) Yamamoto, M.; Iwata, R.; Ishiwata, H.; Yamada, T.; Tanimura, A. *Food Chem. Toxicol.* **1984**, *22*, 61.
- (18) Sen, N. P.; Kushwaha, S. C.; Seaman, S. W.; Clarkson, S. G. *J. Agric. Food. Chem.* **1985**, *33*, 428.
- (19) Song, P. J.; Hu, J. F. *Food Chem. Toxicol.* **1988**, *26*, 205.
- (20) Tomkins, B. A.; Griest, W. H. *Anal. Chem.* **1996**, *68*, 2533.
- (21) Mitch, W. A.; Sharp, J. O.; Trussell, R. R.; Valentine, R. L.; Alvarez-Cohen, L.; Sedlak, D. L. *Environ. Eng. Sci.* **2003**, *20*, 389.
- (22) Charrois, J. W. A.; Arend, M. W.; Froese, K. L.; Hudey, S. E. *Environ. Sci. Technol.* **2004**, *38*, 4835.

- (23) de Vocht, F.; Burstyn, I.; Straif, K.; Vermeulen, R.; Jakobsson, K.; Nichols, L.; Peplonska, B.; Taeger, D.; Kromhout, H. *J. Environ. Monit.* **2007**, *9*, 253.
- (24) Haruta, S.; Chen, W. P.; Gan, J.; Simunek, J.; Chang, A. C.; Wu, L. S. *Ecotoxicol. Environ. Saf.* **2008**, *69*, 374.
- (25) Perez, D. M.; Alatorre, G. G.; Alvarez, E. B.; Silva, E. E.; Alvarado, J. F. J. *Food Chem.* **2008**, *107*, 1348.
- (26) N-Nitrosodimethylamine; CASRN 62-75-9. <http://www.epa.gov/iris/subst/0045.htm>.
- (27) Mirvish, S. S. *Toxicol. Appl. Pharmacol.* **1975**, *31*, 325.
- (28) Challis, B. C.; Shuker, D. E. G. *Food Cosmet. Toxicol.* **1980**, *18*, 283.
- (29) Choi, J.; Valentine, R. L. *Environ. Sci. Technol.* **2003**, *37*, 4871.
- (30) Lv, C. L.; Liu, Y. D.; Wang, Y. H.; Zhong, R. G. *Acta Chim. Sin.* **2007**, *65*, 1568.
- (31) Lv, C. L.; Liu, Y. D.; Zhong, R. G. *J. Phys. Chem. A* **2008**, *112*, 7098.
- (32) Emerson, W. S. *J. Am. Chem. Soc.* **1941**, *63*, 2023.
- (33) Smith, P. A. S.; Pars, H. G. *J. Org. Chem.* **1959**, *24*, 1325.
- (34) Smith, P. A. S.; Loeppky, R. N. *J. Am. Chem. Soc.* **1967**, *89*, 1147.
- (35) Fiddler, W.; Pensabene, J. W.; Doerr, R. C.; Wasserman, A. E. *Nature* **1972**, *236*, 307.
- (36) Lijinsky, W.; Conrad, E.; Van De Bogart, R. *Nature* **1972**, *239*, 165.
- (37) Schweinsberg, F.; Sander, J. *Hoppe-Seyler's Z. Physiol. Chem.* **1972**, *353*, 1671.
- (38) Scanlan, R. A.; Lohsen, S. M.; Bills, D. D.; Libbey, L. M. *J. Agric. Food. Chem.* **1974**, *22*, 149.
- (39) Loeppky, R. N.; Smith, D. H. *J. Org. Chem.* **1976**, *41*, 1578.
- (40) Hecht, S. S.; Chen, C. B.; Orna, R. M.; Jacobs, E.; Adams, J. D.; Hoffmann, D. *J. Org. Chem.* **1978**, *43*, 72.
- (41) Ohshima, H.; Kawabata, T. *IARC Sci. Publ.* **1978**, 143.
- (42) Loeppky, R. N.; Hastings, R.; Sandbothe, J.; Heller, D.; Bao, Y.; Nagel, D. In *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco, and Mycotoxins*; O'Neill, I. K., Chen, J., Bartsch, H., Eds.; IARC Scientific Publications 105; International Agency for Research on Cancer: Lyon, France, 1991; p 244.
- (43) Loeppky, R. N.; Bao, Y. T.; Bae, J. Y.; Yu, L.; Shevlin, G. In *Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry*; ACS Symposium Series 553; American Chemical Society: Washington, D.C., 1994; p 52.
- (44) Itoh, T.; Matsuya, Y.; Maeta, H.; Miyazaki, M.; Nagata, K.; Ohsawa, A. *Chem. Pharm. Bull.* **1999**, *47*, 819.
- (45) Hein, G. E. *J. Chem. Educ.* **1963**, *40*, 181.
- (46) Ohshima, H.; Kawabata, T. *Bull. Jpn. Soc. Sci. Fish.* **1978**, *44*, 77.
- (47) Mitch, W. A.; Sedlak, D. L. *Environ. Sci. Technol.* **2004**, *38*, 1445.
- (48) Mitch, W. A.; Schreiber, M. I. *Environ. Sci. Technol.* **2008**, *42*, 4811.
- (49) Zhang, A. Q.; Mitchell, S. C.; Smith, R. L. *Food Chem. Toxicol.* **1999**, *37*, 515.
- (50) Bain, M. A.; Fornasini, G.; Evans, A. M. *Curr. Drug Metab.* **2005**, *6*, 227.
- (51) Bain, M. A.; Faull, R.; Fornasini, G.; Milne, R. W.; Evans, A. M. *Nephrol. Dial. Transplant.* **2006**, *21*, 1300.
- (52) Malins, D. C.; Roubal, W. T.; Robisch, P. A. *J. Agric. Food. Chem.* **1970**, *18*, 740.
- (53) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
- (54) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
- (55) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
- (56) Montgomery, J. J. A.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A. *J. Chem. Phys.* **1999**, *110*, 2822.
- (57) Klamt, A.; Schuurmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799.
- (58) Noga, J.; Bartlett, R. J. *J. Chem. Phys.* **1987**, *86*, 7041.
- (59) Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2005**, *1*, 70.
- (60) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
- (61) Dahlke, E. E.; Truhlar, D. G. *J. Phys. Chem. B* **2005**, *109*, 15677.
- (62) Csonka, G. I.; Ruzsinszky, A.; Perdew, J. P. *J. Phys. Chem. B* **2005**, *109*, 21471.
- (63) Teuten, E. L.; Loeppky, R. N. *Org. Biomol. Chem.* **2005**, *3*, 1097.
- (64) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
- (65) Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753.
- (66) Kim, C. K.; Lee, I. Y.; Kim, C. K.; Lee, I. *J. Phys. Org. Chem.* **1999**, *12*, 479.

JP9056219

Exhibit 28

FDA STATEMENT

FDA Statement on the FDA's ongoing investigation into valsartan and ARB class impurities and the agency's steps to address the root causes of the safety issues

For Immediate Release:

January 25, 2019

Statement From:

Scott Gottlieb, M.D.



Last summer, the FDA learned and reported that some generic versions of the angiotensin II receptor blocker (ARB) medicines contain nitrosamine impurities that don't meet the agency's safety standards. ARBs, including valsartan, irbesartan, losartan and others, are a class of medicines used to treat high blood pressure and heart failure. Nitrosamine impurities, including N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA), are probable human carcinogens. These two substances are known environmental contaminants and found in water and foods, including meats, dairy products and vegetables. But their presence in drug products is not acceptable.

We were deeply concerned when we learned about the presence of these impurities. We immediately undertook a major operation to investigate and to identify the root causes for the presence of these impurities in some ARB drugs, and to work with companies to address the risks that the impurities pose to patients.

Our analysis of NDMA found that the risk to patients based on the maximum possible exposure appears to be small. That doesn't diminish our concern and our determination to find out how these impurities occurred in the first instance. We're committed to implementing measures to prevent these impurities from occurring in the manufacturing process in the future. Our ultimate goal is to ensure that these impurities are not present in finished drug products, or their components (including active pharmaceutical ingredients, or API).

There remains a great deal of public interest in this matter. Today, we want to provide an update on this ongoing investigation and outline the steps we've taken to identify the root causes of the nitrosamine impurities and to prevent a recurrence of this episode in the future. This continues to be an exhaustive effort led by a multidisciplinary team of chemists, toxicologists, physicians, pharmacists, communication specialists, investigators and analytical laboratory staff from across the FDA and in collaboration with global regulators.

While we're still investigating the root causes of the impurities, our ongoing effort has determined that the impurities may be generated when specific chemicals and reaction conditions are present in the manufacturing process of the drug's API, and may also result from the reuse of materials, such as solvents.

This issue surfaced in the summer of 2018, when the FDA was informed that API manufactured by Zhejiang Huahai Pharmaceutical Co. Ltd. (ZHP), in Linhai, Taizhou Zhejiang China for some generic valsartan-containing medicines contained NDMA, posing a potential safety concern.

Since then, the FDA and additional manufacturers of other ARB medicines have identified more cases of NDMA impurities, as well as NDEA impurities. We've placed a ZHP facility on import alert to stop all its API and finished drugs made using ZHP's API from legally entering the U.S. We also issued them a warning letter outlining several manufacturing violations, including impurity control, change control and cross contamination from one manufacturing process line to another. It's unlikely that the subtle problems causing these impurities could have been found on a routine current good manufacturing practice (CGMP) inspection. Nonetheless, our inspections did reveal systemic problems of supervision that could have created the conditions for quality issues to arise.

We've also worked with manufacturers of all ARB medicines to recall any product that poses a risk to patients. Because of the way API is distributed in the supply chain, one source of contaminated API can impact multiple products. As part of this continuing process, last week, we alerted patients and health care professionals to a voluntary recall of one lot of irbesartan and seven lots of irbesartan and hydrochlorothiazide (HCTZ) combination tablets distributed by Solco Healthcare LLC, a Princeton Pharmaceutical Inc. subsidiary. The recall is due to unacceptable amounts of NDEA in the irbesartan API manufactured by ZHP. We will continue to keep the public updated via our [website \(/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications\)](https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications) of all products being recalled. While we acted aggressively to address the issue once we became aware of it, we must also answer the critical question of, why weren't these impurities detected earlier? We've also been asked whether the FDA could have prevented this from occurring if we had done something differently during surveillance inspections in the preceding years.

We want to lay out the many steps we take to mitigate these kinds of risks.

We engage experts in organic chemistry to detect circumstances that can create the risk for these kinds of impurities to be introduced as a by-product of the manufacturing process or changes made in that process. We also work with international regulators to create standards for mitigating the risk of this type of chemical impurity, known as a “genotoxic” impurity. These chemicals, including NDMA and NDEA, are of special concern to global regulators because, unlike most impurities in drugs, they have the potential to cause harm at very low levels. That’s why we have robust policies and procedures in place to guard against these risks.

In March 2018, the FDA issued a [guidance \(/media/93672/download\)](/media/93672/download) for manufacturers that lays out risk assessments that manufacturers can use to evaluate the presence of genotoxic impurities. This is an internationally-harmonized guidance that regulators and industry have agreed to. The FDA reviews information on impurity testing in product applications and when inspecting facilities. Manufacturers must test for known impurities during their manufacturing processes.

We review information about potential impurities that can occur during manufacturing in applications, including requests that sponsors submit to change some aspects of the manufacturing process, which could create new risks. Specifically, our chemists review applications and referenced information to look for steps and changes where risks could be introduced. To implement a risk assessment for any genotoxic impurity, there must be recognition that it can occur in a product’s manufacturing. The guidance lays out the conditions under which these risks can occur and steps that manufacturers should take to test for these potential impurities. Now that we’ve uncovered the risk of nitrosamine impurities in the manufacturing steps involved in ARBs, we’ll incorporate the findings into ongoing policy development.

In addition to our policy work, the FDA inspects manufacturing facilities worldwide. Generally during CGMP inspections, we review the records that manufacturers must maintain regarding required impurity testing. However, the impact of this record review depends on manufacturers conducting appropriate tests that are capable of detecting the impurity. Tests are selected based on assessments of what impurities may develop as a result of the manufacturing process. In other words, it generally needs to be recognized that there’s a risk of an impurity occurring as a result of a manufacturing process to know the impurity should be tested for.

Our investigation into ZHP’s process identified that a change made to the manufacturing process likely led to this impurity, and that the impurity went undetected by global regulators, including the FDA, for a period of time. Before we undertook this analysis, neither regulators nor industry fully understood how NDMA or NDEA could form during this particular manufacturing process.

This is troubling to us and we know it's troubling to the public. This concern is appropriate. Among other steps, we need to take actions that would prevent a similar situation from occurring. We are making important strides at understanding how these impurities occurred, mitigating the risk to patients and learning what steps need to be taken to prevent this from occurring again in the future.

One challenge we've faced is that NDMA's properties make it hard to detect in standard laboratory testing – the kind of testing results that are reviewed during a surveillance inspection. In St. Louis, the FDA maintains one of the most advanced pharmaceutical laboratories of any regulatory agency in the world. As soon as we became aware of the presence of nitrosamine impurities in certain ARB medicines, we began collecting samples of all ARB API and medicines marketed in the U.S. to test these products specifically for NDMA. More testing found NDEA, also a probable human carcinogen, in other valsartan products and other ARBs from different manufacturers.

During this time, our scientists have developed and refined novel and sophisticated testing methods specifically designed to detect and quantify the NDMA and NDEA in all ARB medicines. We've shared these tests on our website to help manufacturers and other regulators evaluate these products as well. To determine if ARB medicines contain these impurities, FDA scientists developed three testing methods. These include the [GC/MS\) headspace method \(/media/115965/download\)](/media/115965/download), the [combined headspace method \(/media/115965/download\)](/media/115965/download), and the [combined direct injection method \(Combined N-Nitrosodimethylamine \(NDMA\) and N-Nitrosodiethylamine \(NDEA\)\)](#). These testing methods can be used for evaluating both drug substances (API) and finished drug products.

Medicines that contain NDMA or NDEA above [certain limits \(/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan\)](/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan) (see 12/19/2018 update) pose an unacceptable risk to patients, and ARBs that contain impurities above these levels are being recalled. We've also posted lists of [valsartan \(/media/118231/download\)](/media/118231/download), [losartan \(/media/119422/download\)](/media/119422/download), and [irbesartan \(/media/118233/download\)](/media/118233/download) products affected by the recalls. We'll continue to update these lists as new information develops. And we'll continue to work with manufacturers to ensure all affected products are quickly removed from market. We're also working with API makers to ensure that they fix their processes and cease distribution of affected API.

We know patients rely on these medicines. Part of our work throughout this process has been to mitigate and prevent shortages, where possible. Currently, valsartan products are in shortage, and we know that other types of products may fall into shortage soon. That's why the agency has also evaluated safety data for NDMA and NDEA to determine interim acceptable intake levels for

these impurities in the ARB class of medicines. While consumers should limit exposure to NDMA and NDEA, these impurities exist in other ingested products, such as some charcoal grilled food items. And so, our goal is to balance the risk of patients ingesting low levels of the impurities (below the interim acceptable levels) for a short period of time with the risk that there is a shortage of certain ARBs, which may impact patients' ability to access the medicine they need. We remind patients taking these medications or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

Overall, the risk to individual patients remains very small, although this doesn't diminish the significance of this episode or our concerns. FDA scientists estimate that if 8,000 people took the highest daily valsartan dose (320 mg) that contained NDMA, for four years (the time we think the affected products had been on the U.S. market), there may be one additional case of cancer beyond the average cancer rate among those 8,000 Americans. The vast majority of patients exposed to NDMA through ARBs received much smaller amounts of the impurity than this worst-case scenario. Since not all ARBs are affected, it's very likely that a patient taking an ARB for four years would not have always received one of the affected products. We're still seeking to similarly quantify the risk from NDEA and plan to communicate our findings as soon as possible.

Now that these risks are identified, we're applying what we've learned to the evaluation of similar manufacturing processes where we now know these risks could arise. As part of this process, the FDA has identified specific factors in manufacturing processes that may contribute to the formation and presence of NDMA and NDEA. Through our investigation, we're working to ensure that other manufacturing conditions don't contribute to NDMA, NDEA, or related impurities in finished drug products. We'll use the information we've learned about these impurities when reviewing applications, assessing manufacturing changes and conducting inspections. Now that they are aware that certain conditions result in the formation of nitrosamines, manufacturers using processes at risk for these impurities are expected to test for them to ensure that active ingredients and finished products are free of detectable levels of a nitrosamine impurities resulting in drug products that that are safe for patients.

While the total exposure to these impurities for most patients was small, we are deeply concerned that patients were exposed to this impurity in the first place and that the presence of nitrosamines went undetected for a period of time. The potential for the development of genotoxic impurities during manufacturing processes is an area of intense focus. We'll continue to improve our science and standards for detecting and preventing these risks.

We'll also continue to keep the public informed on our [website](#) ([FDA updates on angiotensin II receptor blocker \(ARB\) recalls including valsartan, losartan and irbesartan](#)), which contains most current information. Patients and providers can also send email to druginfo@fda.hhs.gov ([/about-fda/page-not-found](#)) or call 855-543-3784. We're also encouraging submission of any information related to potential side effects to our [MedWatch program](#) ([http://wcms.fda.gov/ucm/resources/wcm/3rdparty/fckeditor/editor/#!/--\\$wcmUrl\('nodelink','2237'\)--](http://wcms.fda.gov/ucm/resources/wcm/3rdparty/fckeditor/editor/#!/--$wcmUrl('nodelink','2237')--))).

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

Inquiries

Media:

✉ [Sarah Peddicord \(mailto:sarah.peddicord@fda.hhs.gov\)](mailto:sarah.peddicord@fda.hhs.gov)

☎ 301-796-2805

Consumer:

☎ 888-INFO-FDA

🔗 [More Press Announcements \(/news-events/newsroom/press-announcements\)](#)

Exhibit 30



U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Via UPS
Return Receipt Requested

December 5, 2022

Mr. David Y.Y. Light
Chief Executive Officer
Valisure, LLC
5 Science Park
New Haven, CT 06511-1966

Dear Mr. Light:

The U.S. Food and Drug Administration (FDA) inspected your drug contract testing laboratory, Valisure, LLC, FEI 3012063246, at 5 Science Park, New Haven, from May 26 to July 6, 2021.

FDA is concerned that Valisure, LLC is not aware of its violations of the drug supply chain security requirements while it owned ValisureRx. The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Drug Supply Chain Security Act (DSCSA), places certain requirements on entities meeting the definition of trading partner. FDA acknowledges the sale of ValisureRx to Medly Health Inc. in April 2021. Until this sale, ValisureRx was a subsidiary of Valisure, LLC. ValisureRx was a licensed pharmacy and wholesale drug distributor, and therefore both a dispenser, as defined by section 581(3) of the FD&C Act, and a wholesale distributor, as defined by section 581(29) of the FD&C Act. ValisureRx was engaged in both wholesale distribution, as defined in section 503(e)(4) of the FD&C Act, and the dispensing of prescription drugs; and therefore was a trading partner under section 581(23) of the FD&C Act.

During FDA's inspection, FDA investigators examined records related to four (4) lots of product that were in Valisure, LLC's possession – including records from the purchase of the product, laboratory testing results, and records of the disposition of the product through a reverse distributor. FDA investigators observed that:

- Your firm failed to investigate suspect product;
- Your firm failed to make determinations of illegitimate product in coordination with the manufacturer; and
- Your firm failed to notify FDA and required trading partners of illegitimate product within 24 hours of such a determination.

During the inspection, FDA investigators observed that ValisureRx did not have systems in place to ensure compliance with the verification requirements of the FD&C Act (sections 582(c)(4)(A) & (B) and (d)(4)(A) & (B)), and in many instances, was not familiar with the requirements of the FD&C Act, as amended by the DSCSA, for wholesale distributors and dispensers.

Section 582(c)(4) and (d)(4) of the FD&C Act establishes the DSCSA's verification requirements for wholesale distributors and dispensers respectively and requires that such trading partners have systems in place to ensure compliance with the verification requirements (FD&C Act sections 582(c)(4)(A) & (B) and (d)(4)(A) & (B)). Among other things, Section 582 requires that product in the possession or control of a wholesale distributor or dispenser which is determined to be a suspect product¹ must be placed into quarantine and not processed further until a determination is made that the product is either cleared or illegitimate² (sections 582(c)(4)(A)(i)(I) and (d)(4)(A)(i)(I) of the FD&C Act). When a product is determined to be a suspect product, prompt investigations must be conducted in coordination with trading partners to determine whether the product is an illegitimate product (section 582(c)(4)(A)(i)(II) and (d)(4)(A)(ii) of the FD&C Act). In addition, the determination of whether a product is an illegitimate product must be made in coordination with the manufacturer (section 582(c)(4)(B)(i) and (d)(4)(B)(i) of the FD&C Act). Finally, if product is determined to be illegitimate product, the trading partner in possession or control of the product must notify FDA and certain trading partners of the illegitimate product within 24 hours of such a determination (section 582(c)(4)(B)(ii) and (d)(4)(B)(ii) of the FD&C Act).

In addition, FDA has observed that Valisure, LLC has never filed an annual report with the FDA as required by section 583(e)(2) of the FD&C Act. This provision requires wholesale distributors to report annually to the FDA each state by which the person is licensed and the name and address of each facility at which the person conducts business. FDA has no records, including in the CDER Direct Electronic Submissions Portal, that Valisure, LLC or ValisureRx reported to the Agency during the time it was engaged in wholesale distribution.

FDA recognizes that since the sale of ValisureRx, Valisure, LLC is no longer a licensed dispenser and that Valisure, LLC was not engaged in wholesale distribution at the time of the inspection. However, we emphasize that if your firm re-engages in such activities, you will be subject to the relevant requirements of the FD&C Act.

Please see the FDA guidance documents listed below for additional information about the DSCSA verification requirements and identifying suspect and illegitimate product under the DSCSA:

- Drug Supply Chain Security Act Implementation: Identification of Suspect Product and Notification, Final Guidance, June 2021, <https://www.fda.gov/media/88790/download>
- Definitions of Suspect Product and Illegitimate Product for Verification Obligations Under the Drug Supply Chain Security Act, Draft Guidance for Industry, June 2021, <https://www.fda.gov/media/111468/download>

¹ *Suspect product* is defined in section 581(21) of the FD&C Act, in part, as "product for which there is reason to believe that such product appears otherwise unfit for distribution such that the product would result in serious adverse health consequences or death to humans."

² *Illegitimate product* is defined in section 581(8) of the FD&C Act, in part, as "product for which credible evidence shows that the product appears otherwise unfit for distribution such that the product would be reasonably likely to result in serious adverse health consequences or death to humans."

- Verification Systems Under the Drug Supply Chain Security Act for Certain Prescription Drugs, Draft Guidance for Industry, March 2022, <https://www.fda.gov/media/117950/download>
- Identifying Trading Partners Under the Drug Supply Chain Security Act, Draft Guidance for Industry, August 2017, <https://www.fda.gov/media/106961/download>

Additional Considerations

Based on the review of documents collected during the inspection, you provide contract testing services for drugs that have been placed into interstate commerce.

Your firm is subject to current good manufacturing practice (CGMP) requirements in that a drug is adulterated if the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of the drug do not meet CGMP as per section 501(a)(2)(B) of the FD&C Act. It is prohibited under the FD&C Act to cause the introduction or delivery for introduction into interstate commerce of an adulterated drug, per section 301(a). It is also prohibited to do any act with respect to a drug that is held for sale after shipment in interstate commerce, if such act results in the drug being adulterated, per section 301(k).

Our inspection found that you provide contract testing services for wholesale distributors and pharmacies that hold drugs for sale after shipment in interstate commerce, including your online pharmacy operation, ValisureRx. We acknowledge that you no longer perform pharmacy operations. You also conduct testing for drug manufacturers, and until recently, your website indicated that your offered services included a “certification process” whereby your testing concludes whether drugs you receive from a manufacturer are “ready for shipment.”³ We acknowledge your explanation in your response to the FDA Form 483 that “passing Valisure testing or obtaining a Valisure certification is not a requirement of drug manufacturing specifications nor FDA approval.” However, we remain concerned that manufacturers may rely on your services in the future to perform contract testing to fulfill CGMP requirements, including those under section 21 CFR part 211.

We also are concerned that your distributor and pharmacy clients, despite not being obligated to perform the same type of release testing required of finished dosage form manufacturers under CGMP, may rely on your testing while a drug is held for sale, to inform their decision to further place a drug into interstate commerce. This letter summarizes scientific deficiencies in your test methods.

Methodological Deficiencies

During our inspection, our investigators observed methodological deficiencies including, but not limited to, the following.

³ Valisure website as of April 13, 2022

1. Your firm failed to establish and document the accuracy, sensitivity, specificity, and reproducibility of its test methods.

You did not demonstrate the analytical methods used to generate Certificates of Analysis (COAs) provided to your customers were suitable. For example,

- Your laboratory used the FDA's Gas Chromatography-Mass Spectrometry (GC-MS) method developed for the detection of N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in valsartan drug products.⁴ However, you were using this method to detect additional impurities (e.g. (b) (4), dimethylformamide (DMF), N-nitrosoethylisopropylamine (NEIPA), N-nitrosodiisopropylamine (NDIPA) and N-nitrosomethylethylamine (NMEA)), and were using this method for other drug products (e.g. (b) (4), (b) (4), (b) (4)) for which the method was not developed. Your firm failed to validate that this method can adequately detect these additional impurities in the drug products you analyzed. The FDA has previously communicated concerns about your inadequate data to support the use of FDA's GC-MS method for detecting impurities in drug products for which the method was not developed.⁵
- Your laboratory used the FDA's Liquid Chromatography High Resolution Mass Spectrometry (LC-HRMS) method developed for the detection of six nitrosamines in angiotensin II receptor blocker (ARB) drugs.⁶ However, you used this method to additionally detect DMF and (b) (4) and to analyze other drug products including (b) (4), (b) (4), (b) (4), and (b) (4), for which the method had not been developed. You could not provide appropriate scientific studies and method validation results to support the use of this method for other drugs. The FDA has previously communicated concerns about the inadequate validation of your method for detection of NDMA in metformin.⁷

The verification of United States Pharmacopeia (USP) compendial methods was also inadequate. For example,

- Your laboratory used a modified version of the USP <467> GC-MS method for the detection of residual solvents, including (b) (4), (b) (4), and (b) (4). You failed to

⁴ FDA Analytical Method: FDA FY19-005-DPA-S "Combined N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) Impurity Assay by GC/MS-Headspace" (01/28/2019), <https://www.fda.gov/media/117843/download>

⁵ FDA has expressed concern with your nitrosamine analyses in previous correspondence, specifically with your use of FDA's GC-MS headspace method FY 19-005-DPA (appropriate for angiotensin II receptor blocker (ARBs)) for the analysis of ranitidine which causes the heat mediated degradation of the drug substance and artificially high levels of NDMA, <https://www.regulations.gov/document/FDA-2019-P-4281-0008>, "Final Response Letter from FDA CDER to Valisure, LLC", April 1, 2020, Footnote 43

⁶ Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of Six Nitrosamine Impurities in ARB Drugs (05/21/2019), <https://www.fda.gov/media/125478/download>

⁷ In the Citizen Petition Response, dated June 20, 2020, the FDA noted that Valisure did not perform sufficient studies to account for interfering substances such as DMF and could not meet the validation standard for specificity: <https://www.regulations.gov/document/FDA-2020-P-0978-0009>

provide adequate validation data for the modifications you made to the compendial. Likewise, liquid and gel (b) (4) drug products were analyzed using this unvalidated method without considering matrix effects.

- Your laboratory used a modified Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) method based on USP <232> and <233>. You did not provide adequate supportive validation data for the use of this modified method, including accuracy, spike and recovery, precision, and linearity per USP <233>.
- Your laboratory used a single High Performance Liquid Chromatography (HPLC) method for assay determination. You could not provide adequate supportive validation data for the use of this single method for assay determination of dextromethorphan hydrobromide, fexofenadine hydrochloride, and other drugs.

In addition, other analytical discrepancies were noted during the inspection and during the review of documents collected:

- Your methods, including GC-MS, ICP-MS, and HPLC, did not require a determination of system suitability prior to analysis, as per USP <621>.
- For nitrosamine determination by GC-MS, calibration standards were not run with the samples, and instead you relied on a calibration curve previous saved to the analytical system to quantify impurities. There was no established frequency for determining the calibration curve. Your laboratory manager stated that calibration may only be done when there is a column change or when instability is observed in the system.
- You did not provide stability data to support assay sample preparation by (b) (4) (b) (4) milling or compatibility data to support use of a (b) (4) um (b) (4) centrifuge filter during assay sample preparation.
- During FDA's review of HPLC chromatograms collected during the inspection, we determined that an incorrect baseline construction had been used for fexofenadine HCl lot # S200622 which resulted in inaccurate integration. Incorrect integration may lead to larger peak area and overestimation of assay and impurity concentrations for drugs.

In your response, you stated that your methods are accurate and reliable pursuant of International Organization for Standardization (ISO) procedures and failed to provide any supportive evidence or reports that your methods have been validated, verified, or suitable for use to support fulfillment of CGMP requirements, such as release decisions of drugs into interstate commerce.

Under CGMP, test methods used by manufacturers for drug product release decisions must be validated⁸ for each drug product that will be tested using an analytical method. At a minimum, method validation experiments should include specificity, accuracy, precision (repeatability and intermediate precision), linearity, range, and limit of quantitation.

⁸ See 21 CFR 211.165(e)

For FDA's current thinking about the validation of analytical methods see, FDA's *Analytical Procedures and Methods Validation for Drugs and Biologics Guidance for Industry* (July 2015): <https://www.fda.gov/media/87801/download>.

2. Your firm does not adequately address out-of-specification (OOS) test results.

You lack written procedures to govern the investigation of out of specification (OOS) results, including identification of adequate corrective action and preventive actions (CAPAs). For example, following the failure of an ICP-MS lead analysis for (b) (4) lot number (b) (4), you changed the tube digestion procedure and re-analyzed the sample without performing an OOS laboratory investigation or determining that the second digestion and re-analysis procedure were appropriate. Likewise, while your firm maintains a log of OOS results and corrective actions taken, your firm failed to provide adequate justification and evidence that these actions would be effective for resolving instrument, method, or other laboratory deviations observed.

Your laboratory manager stated that if the GC-MS method for nitrosamine impurities yields an OOS result, then the sample is analyzed by LC-MS. If the sample passes using the second LC-MS method, then the original OOS result is invalidated without an investigation. Your Chief Executive Officer confirmed this two-tier testing approach. You lack adequate justification for systematically invalidating OOS results when OOS results are found using your method. All test results, passing and failing, should be reported to your quality management system for review and provided to your customers for consideration when releasing drug products in interstate commerce.

For more information about handling failing, OOS, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production* for appropriately handling OOS and performing investigations at: <https://www.fda.gov/media/71001/download>

3. Your firm used instruments, apparatus, gauges, and/or recording devices that did not meet established specifications.

Your analytical instruments have not been adequately qualified for the testing performed. Equipment qualification had not been completed for the GC-MS, LC-HRMS, UPLC, and ICP-MS. For example, although you provided installation and operational qualification documents supplied by your ICP-MS instrument vendor, you did not provide sufficient evidence that the equipment was qualified for its intended purpose and could robustly perform the required operations.

In your response to the FDA Form 483, you stated that (b) (4) and routine maintenance is performed and that you maintain "objective evidence that [Valisure, LLC's] equipment can correctly perform all testing specified in the certifications [Valisure, LLC] provides." However, this information was not provided. In addition, your practice of assessing standard injections in advance of sample analysis is inadequate to demonstrate that the equipment can robustly perform the intended testing operations over the equipment lifetime.

4. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records.

Your firm lacks controls to assure that analytical data is accurately processed, reviewed, and retained. While the software controlling your analytical equipment requires unique user accounts and passwords, your analysts log into the operating computers using a generic administrator account such as “Valisure” or “Valisure Lab.” Controls are not in place to prevent the deletion of data from these administrator accounts.

Further, controls are not in place to ensure the accuracy of reported data results. When testing is completed, your analysts enter numeric values into a cloud database as the final result for the testing performed. Your firm could not provide associated procedures to review raw data, automated or manual data processing, or audit trails. You could not provide evidence of supervisory review of the testing performed.

Your response only addressed analyst accounts and access levels within the analytical software. You failed to address controls over the operating system which could allow for creation, modification, and deletion of data.

See FDA’s guidance document *Data Integrity and Compliance With Drug CGMP* for guidance on establishing and following CGMP compliant data integrity practices at:

<https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf> and <https://www.fda.gov/media/119267/download>

Responsibilities of a Contract Testing Lab

As noted above, FDA documented that your website previously indicated the capability to test drugs in support of shipment release decisions, including for drug product manufacturers. Contract laboratories that perform testing for drug manufacturing facilities must meet applicable CGMP requirements. See FDA’s guidance document *Contract Manufacturing Arrangements for Drugs: Quality Agreements*, (November 2016) at <https://www.fda.gov/media/86193/download>.

Your Response to the FDA Form 483

In your response to the FDA Form 483 you stated that Valisure, LLC’s testing is “only for informational and marketing purpose and not for any regulatory purpose.” Additionally, you stated that your testing “is not subject to the cGMP standards set forth by FDA.” You state that the purpose of your testing is to “broadly screen medicinal products” and that Valisure, LLC “does not typically run product-specific methodologies.” Lastly, you stated, “Valisure’s services are not intended for and not appropriate for any regulatory purpose.” However, FDA is concerned that entities will use your test results for CGMP purposes.

If you intend to test drugs for purposes of fulfilling CGMP obligations, we recommend you perform a gap assessment to ensure you comply with CGMP. If you would like to meet with the

FDA to discuss minimal CGMP expectations, please contact CDER-OC-OMQ-Communications@fda.hhs.gov to schedule a meeting.

Valisure, LLC's Use of ISO Standard 17025

In your response to the FDA Form 483, you stated that Valisure, LLC's laboratory is accredited to the ISO 17025 standard⁹ to ensure the testing conducted by Valisure, LLC is reliable and accurate. While there is value in accreditation to the ISO 17025 standard, FDA is concerned that potential clients who may use your services to support fulfillment of CGMP obligations may be unaware that ISO 17025 accreditation alone does not mean you are operating in compliance with CGMP requirements for the analytical testing of drugs subject to CGMP. Additionally, while you provided a copy of your ISO 17025 accreditation, based on the technical concerns described above, Valisure, LLC appears to deviate significantly from the ISO 17025 standard.

Conclusion

The deficiencies cited in this letter are not intended to be an all-inclusive list of those that exist at your facility. You are responsible for investigating and determining the causes of any deficiencies and for preventing their recurrence.

This letter notifies you of our findings and provides you an opportunity to address them. After you receive this letter, please respond to this office in writing within 30 working days. Specify what you have done to address any deficiencies identified above and to prevent their recurrence.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov. Identify your response with FEI 3012063246.

Sincerely,

/s/

Jill P. Furman
Acting Director
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

⁹ ISO/IEC 17025:2017 "General requirements for the competence of testing and calibration laboratories"

Exhibit 32

GENERAL NOTICES AND REQUIREMENTS

The *General Notices and Requirements* section (the *General Notices*) presents the basic assumptions, definitions, and default conditions for the interpretation and application of the *United States Pharmacopeia* (USP) and the *National Formulary* (NF).

Requirements stated in these *General Notices* apply to all articles recognized in the *USP* and *NF* (the “compendia”) and to all general chapters unless specifically stated otherwise. Where the requirements of an individual monograph differ from the *General Notices* or a general chapter, the monograph requirements apply and supersede the requirements of the *General Notices* or the general chapter, whether or not the monograph explicitly states the difference.

1. TITLE AND REVISION

The full title of this publication (consisting of four volumes and including its *Supplements*), is *The Pharmacopeia of the United States of America*, Thirty-Eighth Revision and the *National Formulary*, Thirty-Third Edition. These titles may be abbreviated to *USP 38*, to *NF 33*, and to *USP 38–NF 33*. The *United States Pharmacopeia*, Thirty-Eighth Revision, and the *National Formulary*, Thirty-Third Edition, supersede all earlier revisions. Where the terms “*USP*,” “*NF*,” or “*USP–NF*” are used without further qualification during the period in which these compendia are official, they refer only to *USP 38*, *NF 33*, and any *Supplement(s)* thereto. The same titles, with no further distinction, apply equally to print or electronic presentation of these contents. Although *USP* and *NF* are published under one cover and share these *General Notices*, they are separate compendia.

This revision is official beginning April 1, 2015, unless otherwise indicated in specific text.

Supplements to *USP* and *NF* are published periodically.

Interim Revision Announcements are revisions to *USP* and *NF* that are published on the USP website. *Interim Revision Announcements* contain official revisions and their effective dates. Announcements of the availability of new USP Reference Standards and announcements of tests or procedures that are held in abeyance pending availability of required USP Reference Standards are also available on the “New Official Text” tab of USP’s website.

Revision Bulletins are revisions to official text or postponements that require expedited publication. They are published on the USP website and generally are official immediately unless otherwise specified in the *Revision Bulletin*.

Errata are corrections to items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirements.

2. OFFICIAL STATUS AND LEGAL RECOGNITION

2.10. Official Text

Official text is text contained in *USP* and *NF*, including monographs, general chapters, and these *General Notices*. Revisions to official text are provided in *Supplements*, *Interim Revision Announcements*, and *Revision Bulletins*. General chapters numbered from 1000 to 1999 are considered interpretive and are intended to provide information on, give definition to, or describe a particular subject. They contain no mandatory requirements applicable to any official article unless specifically referenced in *General Notices*, a mono-

graph, or a general chapter numbered below 1000. General chapters numbered above 2000 apply only to articles that are intended for use as dietary ingredients and dietary supplements.

2.20. Official Articles

An *official article* is an article that is recognized in *USP* or *NF*. An article is deemed to be recognized and included in a compendium when a monograph for the article is published in the compendium and an official date is generally or specifically assigned to the monograph.

The title specified in a monograph is the *official title* for such article. Other names considered to be synonyms of the official titles may not be used as substitutes for official titles.

Official articles include both *official substances* and *official products*. An *official substance* is a drug substance, excipient, dietary ingredient, other ingredient, or component of a finished device for which the monograph title includes no indication of the nature of the finished form.

An *official product* is a drug product, dietary supplement, compounded preparation, or finished device for which a monograph is provided.

2.30. Legal Recognition

The *USP* and *NF* are recognized in the laws and regulations of many countries throughout the world. Regulatory authorities may enforce the standards presented in the *USP* and *NF*, but because recognition of the *USP* and *NF* may vary by country, users should understand applicable laws and regulations. In the United States under the Federal Food, Drug, and Cosmetic Act (FDCA), both *USP* and *NF* are recognized as official compendia. A drug with a name recognized in *USP–NF* must comply with compendial identity standards or be deemed adulterated, misbranded, or both. See, e.g., FDCA § 501(b) and 502(e)(3)(b); also FDA regulations, 21 CFR § 299.5(a&b). To avoid being deemed adulterated, such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs. See, e.g., FDCA § 501(b) and 21 CFR § 299.5(c). In addition, to avoid being deemed misbranded, drugs recognized in *USP–NF* must also be packaged and labeled in compliance with compendial standards. See FDCA § 502(g).

A dietary supplement represented as conforming to specifications in *USP* will be deemed a misbranded food if it fails to so conform. See FDCA § 403(s)(2)(D).

Enforcement of *USP* standards is the responsibility of FDA and other government authorities in the U.S. and elsewhere. *USP* has no role in enforcement.

3. CONFORMANCE TO STANDARDS

3.10. Applicability of Standards

Standards for an article recognized in the compendia (*USP–NF*) are expressed in the article’s monograph, applicable general chapters, and *General Notices*. Unless specifically exempted elsewhere in a compendium, the identity, strength, quality, and purity of an article are determined by the official tests, procedures, and acceptance criteria, whether incorporated in the monograph itself, in the *General Notices*, or in the applicable general chapters. Early adoption of revised standards is allowed. Where revised

2 General Notices

standards for an existing article have been published as final approved "official text" (as approved in section 2.10) but are not yet official (six months after publication, unless otherwise specified; see "official date," section 2.20), compliance with the revised standard shall not preclude a finding or indication of conformance with compendial standards, unless USP specifies otherwise by prohibiting early adoption in a particular standard.

The standards in the relevant monograph, general chapter(s), and *General Notices* apply at all times in the life of the article from production to expiration. The manufacturer's specifications, and good manufacturing practices generally (including, e.g., Quality by Design initiatives), are developed and followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed. Thus, any official article is expected to meet the compendial standards if tested, and any official article actually tested as directed in the relevant monograph must meet such standards to demonstrate compliance.

At times, compendial standards take on the character of statistical procedures, with multiple units involved and perhaps a sequential procedural design to allow the user to determine that the tested article meets or does not meet the standard. The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. Frequency of testing and sampling are left to the preferences or direction of those performing compliance testing, and other users of *USP-NF*, including manufacturers, buyers, or regulatory authorities.

Official products are prepared according to recognized principles of good manufacturing practice and from ingredients that meet *USP* or *NF* standards, where standards for such ingredients exist (for dietary supplements, see section 3.10.20).

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs.

3.10.10. Applicability of Standards to Drug Products, Drug Substances, and Excipients

The applicable *USP* or *NF* standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. Such articles (drug products, drug substances, and excipients) include both human drugs (whether dispensed by prescription, "over the counter," or otherwise), as well as animal drugs. The applicable standard applies to such articles whether or not the added designation "*USP*" or "*NF*" is used. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, or where there is use of synonyms with the intent or effect of suggesting a significant degree of identity with the official title or name.

3.10.20. Applicability of Standards to Medical Devices, Dietary Supplements, and Their Components and Ingredients

An article recognized in *USP* or *NF* shall comply with the compendial standards if the article is a medical device, component intended for a medical device, dietary supplement, dietary ingredient, or other ingredient that is in-

tended for incorporation into a dietary supplement, and is labeled as conforming to the *USP* or *NF*.

Generally, dietary supplements are prepared from ingredients that meet *USP*, *NF*, or *Food Chemicals Codex* standards. Where such standards do not exist, substances may be used in dietary supplements if they have been shown to be of acceptable food grade quality using other suitable procedures.

3.20. Indicating Conformance

A drug product, drug substance, or excipient may use the designation "*USP*" or "*NF*" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article complies with the identity prescribed in the specified compendium.

When a drug product, drug substance, or excipient differs from the relevant *USP* or *NF* standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.

When a drug product, drug substance, or excipient fails to comply with the identity prescribed in *USP* or *NF* or contains an added substance that interferes with the prescribed tests and procedures, the article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in *USP* or *NF*.

A medical device, dietary supplement, or ingredient or component of a medical device or dietary supplement may use the designation "*USP*" or "*NF*" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article complies with the monograph standards and other applicable standards in the compendium.

The designation "*USP*" or "*NF*" on the label may not and does not constitute an endorsement by *USP* and does not represent assurance by *USP* that the article is known to comply with the relevant standards. *USP* may seek legal redress if an article purports to be or is represented as an official article in one of *USP*'s compendia and such claim is determined by *USP* not to be made in good faith.

The designation "*USP-NF*" may be used on the label of an article provided that the label also bears a statement such as "Meets *NF* standards as published by *USP*," indicating the particular compendium to which the article purports to apply.

When the letters "*USP*," "*NF*," or "*USP-NF*" are used on the label of an article to indicate compliance with compendial standards, the letters shall appear in conjunction with the official title of the article. The letters are not to be enclosed in any symbol such as a circle, square, etc., and shall appear in capital letters.

If a dietary supplement does not comply with all applicable compendial requirements but contains one or more dietary ingredients or other ingredients that are recognized in *USP* or *NF*, the individual ingredient(s) may be designated as complying with *USP* or *NF* standards or being of *USP* or *NF* quality provided that the designation is limited to the individual ingredient(s) and does not suggest that the dietary supplement complies with *USP* standards.

4. MONOGRAPHS AND GENERAL CHAPTERS

4.10. Monographs

Monographs set forth the article's name, definition, specification, and other requirements related to packaging, storage, and labeling. The specification consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality, and purity of the article. For general requirements relating to specific monograph sections, see section 5, *Monograph Components*.

Because monographs may not provide standards for all relevant characteristics, some official substances may con-

Revision Bulletin

Official April 1, 2015

General Notices 3

form to the *USP* or *NF* standard but differ with regard to nonstandardized properties that are relevant to their use in specific preparations. To assure interchangeability in such instances, users may wish to ascertain functional equivalence or determine such characteristics before use.

4.10.10. Applicability of Test Procedures

A single monograph may include several different tests, procedures, and/or acceptance criteria that reflect attributes of different manufacturers' articles. Such alternatives may be presented for different polymorphic forms, impurities, hydrates, and dissolution cases. Monographs indicate the tests, procedures, and/or acceptance criteria to be used and the required labeling.

A test in a monograph may contain and require multiple procedures. However, multiple procedures may be included in particular monographs specifically for the purpose of assuring the availability of an appropriate procedure for a particular product. In such cases, a labeling statement to indicate the appropriate application of the procedure(s) will be included in the monograph. A labeling statement is not required if Test 1 is used.

4.10.11. Dissolution, Disintegration, and Drug Release Tests

Multiple Dissolution, Disintegration, or Drug Release tests may be present in the monograph. The order in which the tests are listed in the monograph is based on the order in which they are approved by the relevant Expert Committee for inclusion in the monograph. Test 1 is not necessarily the test for the innovator or for the reference product. Compliance with any of the tests does not assure bioequivalence or bioavailability.

4.10.20. Acceptance Criteria

The acceptance criteria allow for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. The existence of compendial acceptance criteria does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" compendial quality. Similarly, the fact that an article has been prepared to tighter criteria than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the compendial requirements.

An official product shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. Where the minimum amount of a substance present in a dietary supplement is required by law to be higher than the lower acceptance criterion allowed for in the monograph, the upper acceptance criterion contained in the monograph may be increased by a corresponding amount.

The acceptance criteria specified in individual monographs and in the general chapters for compounded preparations are based on such attributes of quality as might be expected to characterize an article compounded from suitable bulk drug substances and ingredients, using the procedures provided or recognized principles of good compounding practice, as described in these compendia.

4.20. General Chapters

Each general chapter is assigned a number that appears in angle brackets adjacent to the chapter name (e.g., *Chromatography* <621>). General chapters may contain the following:

- Descriptions of tests and procedures for application through individual monographs,
- Descriptions and specifications of conditions and practices for pharmaceutical compounding,
- General information for the interpretation of the compendial requirements,
- Descriptions of general pharmaceutical storage, dispensing, and packaging practices, or

- General guidance to manufacturers of official substances or official products.

When a general chapter is referenced in a monograph, acceptance criteria may be presented after a colon.

Some chapters may serve as introductory overviews of a test or of analytical techniques. They may reference other general chapters that contain techniques, details of the procedures, and, at times, acceptance criteria.

Change to read:**5. MONOGRAPH COMPONENTS****5.10. Molecular Formula**

The use of the molecular formula for the active ingredient(s) named in defining the required strength of a compendial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

5.20. Added Substances

Added substances are presumed to be unsuitable for inclusion in an official article and therefore prohibited, if: (1) they exceed the minimum quantity required for providing their intended effect; (2) their presence impairs the bioavailability, therapeutic efficacy, or safety of the official article; or (3) they interfere with the assays and tests prescribed for determining compliance with the compendial standards.

The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.

5.20.10. Added Substances, Excipients, and Ingredients in Official Substances

Official substances may contain only the specific added substances that are permitted by the individual monograph. Where such addition is permitted, the label shall indicate the name(s) and amount(s) of any added substance(s).

5.20.20. Added Substances, Excipients, and Ingredients in Official Products

Suitable substances and excipients such as antimicrobial agents, pharmaceutical bases, carriers, coatings, flavors, preservatives, stabilizers, and vehicles may be added to an official product to enhance its stability, usefulness, or elegance, or to facilitate its preparation, unless otherwise specified in the individual monograph.

Added substances and excipients employed solely to impart color may be incorporated into official products other than those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the U.S. Food and Drug Administration (FDA), provided such added substances or excipients are otherwise appropriate in all respects. (See also *Injections* <1>, *Ingredients, Vehicles and Added Substances, Added Substances*.)

The proportions of the substances constituting the base in ointment and suppository products and preparations may be varied to maintain a suitable consistency under different climatic conditions, provided that the concentrations of active ingredients are not varied and provided that the bioavailability, therapeutic efficacy, and safety of the preparation are not impaired.

5.20.20.1. In Compounded Preparations

Compounded preparations for which a complete composition is given shall contain only the ingredients named in the formulas unless specifically exempted herein or in the individual monograph. Deviation from the specified processes or methods of compounding, although not from the ingredients or proportions thereof, may occur provided

4 General Notices

that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process.

Where a monograph for a compounded preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried before use if due allowance is made for the water or other volatile substances present in the quantity taken.

Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of official preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A preparation that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a usual ingredient in the preparation or a permissible added substance; in either case the denaturant shall be identified on the label of the topical preparation. Where a process is given in the individual monograph, any preparation compounded using denatured alcohol shall be identical to that prepared by the monograph process.

5.20.20.2. In Dietary Supplements

Additional ingredients may be added to dietary supplement products provided that the additional ingredients: (1) comply with applicable regulatory requirements; and (2) do not interfere with the assays and tests prescribed for determining compliance with compendial standards.

5.30. Description and Solubility

Only where a quantitative solubility test is given in a monograph and is designated as such is it a test for purity.

A monograph may include information regarding the article's description. Information about an article's "description and solubility" also is provided in the reference table *Description and Relative Solubility of USP and NF Articles*. The reference table merely denotes the properties of articles that comply with monograph standards. The reference table is intended primarily for those who use, prepare, and dispense drugs and/or related articles. Although the information provided in monographs and the information in the reference table may indirectly assist in the preliminary evaluation of an article, it is not intended to serve as a standard or test for purity.

The approximate solubility of a compendial substance is indicated by one of the following descriptive terms:

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble, or Insoluble	Greater than or equal to 10,000

5.40. Identity

A compendial test titled *Identity* or *Identification* is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers, and to establish whether it is the article named in *USP–NF*. The *Identity* or *Identification* test for a particular article may consist of one or more procedures. When a compendial test for *Identity* or *Identification* is undertaken, all requirements of all specified procedures in the test must be met to satisfy the requirements of the test. Failure of an article to meet all the requirements of a prescribed *Identity*

or *Identification* test (i.e., failure to meet the requirements of all of the specified procedures that are components of that test) indicates that the article is mislabeled and/or adulterated.

5.50. Assay

Assay tests for compounded preparations are not intended for evaluating a compounded preparation before dispensing, but instead are intended to serve as the official test in the event of a question or dispute regarding the preparation's conformance to official standards.

5.50.10. Units of Potency (Biological)

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as "USP Units." For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not International Units or USP Units have been defined (see *Biologics* <1041>).

5.60. Impurities and Foreign Substances

Tests for the presence of impurities and foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Drug Substances and Drug Products* <1086>).

Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practices.

5.60.10. Other Impurities in USP and NF Articles

If a *USP* or *NF* monograph includes an assay or organic impurity test based on chromatography, other than a test for residual solvents, and that monograph procedure does not detect an impurity present in the substance, the amount and identity of the impurity, where both are known, shall be stated in the labeling (certificate of analysis) of the official substance, under the heading *Other Impurity(ies)*.

The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater. The sum of all *Other Impurities* combined with the monograph-detected impurities may not exceed 2.0% (see *Ordinary Impurities* <466>), unless otherwise stated in the monograph.

The following categories of drug substances are excluded from *Other Impurities* requirements:

- Fermentation products and semi-synthetics derived therefrom,
- Radiopharmaceuticals,
- Biologics,
- Biotechnology-derived products,
- Peptides,
- Herbals, and
- Crude products of animal or plant origin.

Any substance known to be toxic shall not be listed under *Other Impurities*.

5.60.20. Residual Solvents in USP and NF Articles

All *USP* and *NF* articles are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. If solvents are used during production,

Revision Bulletin

Official April 1, 2015

General Notices 5

they must be of suitable quality. In addition, the toxicity and residual level of each solvent shall be taken into consideration, and the solvents limited according to the principles defined and the requirements specified in *Residual Solvents* (467), using the general methods presented therein or other suitable methods.

5.60.30. Elemental Impurities in USP Drug Products and Dietary Supplements

Effective January 1, 2018, elemental impurities will be controlled in official drug products according to the principles defined and requirements specified in *Elemental Impurities—Limits* (232). Effective January 1, 2018, elemental contaminants are controlled in official dietary supplements according to the principles defined and requirements specified in *Elemental Contaminants in Dietary Supplements* (2232). Also effective January 1, 2018, general chapter *Heavy Metals* (231) will be omitted and all references to it in general chapters and monographs will be deleted. Early adoption of the requirements in (232) and (2232) are permitted by USP, and if (232) or (2232), as applicable, is fully implemented with respect to a particular drug product or dietary supplement in advance of the January 1, 2018 date, that product and its ingredients will no longer need to comply with applicable (231) requirements to be considered by USP to be in conformance with *USP–NF* requirements. • (RB 1-Apr-2015)

5.70. Performance Tests

Where content uniformity determinations have been made using the same analytical methodology specified in the *Assay*, with appropriate allowances made for differences in sample preparation, the average of all of the individual content uniformity determinations may be used as the *Assay* value.

5.80. USP Reference Standards

USP Reference Standards are authentic specimens that have been approved as suitable for use as comparison standards in *USP* or *NF* tests and assays. (See *USP Reference Standards* (11).) Where *USP* or *NF* tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive. Where a procedure calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article shall be used. If any new *USP* or *NF* standard requires the use of a new USP Reference Standard that is not yet available, that portion of the standard containing the requirement shall not be official until the specified USP reference material is available.

Unless a Reference Standard label bears a specific potency or content, assume the Reference Standard is 100.0% pure in the official application. Unless otherwise directed in the procedure in the individual monograph or in a general chapter, USP Reference Standards are to be used in accordance with the instructions on the label of the Reference Standard.

Change to read:**6. TESTING PRACTICES AND PROCEDURES****6.10. Safe Laboratory Practices**

In performing compendial procedures, safe laboratory practices shall be followed, including precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures used. Before undertaking any procedure described in the compendia, the analyst should be aware of the hazards associated with the chemicals and the techniques and means of protecting against them. These compendia are not designed to describe such hazards or protective measures.

6.20. Automated Procedures

Automated and manual procedures employing the same basic chemistry are considered equivalent.

6.30. Alternative and Harmonized Methods and Procedures

Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances. Such alternative procedures and methods shall be validated as described in the general chapter *Validation of Compendial Procedures* (1225) and must be shown to give equivalent or better results. Only those results obtained by the methods and procedures given in the compendium are conclusive.

Alternative procedures should be submitted to USP for evaluation as a potential replacement or addition to the standard (see section 4.10, *Monographs*).

Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method or procedure from one of these pharmacopoeias, it should comply with the requirements of the *USP–NF*. When a difference appears, or in the event of dispute, only the result obtained by the method and/or procedure given in the *USP–NF* is conclusive.

6.40. Dried, Anhydrous, Ignited, or Solvent-Free Basis

All calculations in the compendia assume an “as-is” basis unless otherwise specified.

Test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on Drying*, or *Water Determination*, or *Loss on Ignition*, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

The term “solvent-free” signifies that the calculation shall be corrected for the presence of known solvents as determined using the methods described in *Residual Solvents* (467) unless a test for limit of organic solvents is provided in the monograph.

The term “previously dried” without qualification signifies that the substance shall be dried as directed under *Loss on Drying* (731) or *Water Determination* (921) (gravimetric determination).

Where drying in vacuum over a desiccant is directed, a vacuum desiccator, a vacuum drying pistol, or other suitable vacuum drying apparatus shall be used.

6.40.10. Ignite to Constant Weight

“Ignite to constant weight” means that ignition shall be continued at $800 \pm 25^\circ$, unless otherwise indicated, until two consecutive weighings, the second of which is taken after an additional period appropriate to the nature and quantity of the residue, do not differ by more than 0.50 mg per g of substance taken.

6.40.20. Dried to Constant Weight

“Dried to constant weight” means that drying shall be continued until two consecutive weighings, the second of which is taken after an additional drying period appropriate to the nature and quantity of the residue, do not differ by more than 0.50 mg per g of substance taken.

6.50. Preparation of Solutions**6.50.10. Filtration**

Where a procedure gives direction to “filter” without further qualification, the liquid shall be passed through suitable filter paper or equivalent device until the filtrate is clear.

6 General Notices

Due to the possibility of filter effects, the initial volumes of a filtrate may be discarded.

6.50.20. Solutions

Unless otherwise specified, all solutions shall be prepared with Purified Water. Solutions for quantitative measures shall be prepared using accurately weighed or accurately measured analytes (see section 8.20, *About*).

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid shall be diluted with, or 1 part *by weight* of a solid shall be dissolved in, a sufficient quantity of the diluent or solvent to make the volume of the finished solution 10 parts *by volume*. An expression such as "(20:5:2)" means that the respective numbers of parts, *by volume*, of the designated liquids shall be mixed, unless otherwise indicated.

6.50.20.1. Adjustments to Solutions

When a specified concentration is called for in a procedure, a solution of other normality or molarity may be used, provided that allowance is made for the difference in concentration and that the change does not increase the error of measurement.

Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy.

Unless otherwise indicated, analyte concentrations shall be prepared to within ten percent (10%) of the indicated value. In the special case in which a procedure is adapted to the working range of an instrument, solution concentrations may differ from the indicated value by more than ten percent (10%), with appropriate changes in associated calculations. Any changes shall fall within the validated range of the instrument.

When adjustment of pH is indicated with either an acid or base and the concentration is not indicated, appropriate concentrations of that acid or base may be used.

6.50.20.2. Test Solutions

Information on Test Solutions (TS) is provided in the *Test Solutions* portion of the *Reagents, Indicators, and Solutions* section of the *USP–NF*. Use of an alternative Test Solution or a change in the Test Solution used may require validation.

6.50.20.3. Indicator Solutions

Where a procedure specifies the use of an indicator TS, approximately 0.2 mL, or 3 drops, of the solution shall be added unless otherwise directed.

6.60. Units Necessary to Complete a Test

Unless otherwise specified, a sufficient number of units to ensure a suitable analytical result shall be taken.

6.60.10. Tablets

Where the procedure of a Tablet monograph directs to weigh and finely powder not fewer than a given number of Tablets, a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered Tablets taken shall be representative of the whole Tablets and shall, in turn, be weighed accurately.

6.60.20. Capsules

Where the procedure of a Capsule monograph gives direction to remove, as completely as possible, the contents of not fewer than a given number of the Capsules, a counted number of Capsules shall be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken shall be representative of the contents of the Capsules and shall, in turn, be weighed accurately.

6.70. Reagents

The proper conduct of the compendial procedures and the reliability of the results depend, in part, upon the quality of the reagents used in the performance of the procedures. Unless otherwise specified, reagents conforming to the specifications set forth in the current edition of *Reagent*

Chemicals published by the American Chemical Society (ACS) shall be used. Where such ACS reagent specifications are not available or where the required purity differs, compendial specifications for reagents of acceptable quality are provided (see the *Reagents, Indicators, and Solutions* section of the *USP–NF*). Reagents not covered by any of these specifications should be of a grade suitable to the proper performance of the method of assay or test involved.

Listing of these reagents, including the indicators and solutions employed as reagents, in no way implies that they have therapeutic utility; furthermore, any reference to *USP* or *NF* in their labeling shall include also the term "reagent" or "reagent grade." *USP* may supply reagents if they otherwise may not be generally commercially available.

6.80. Equipment

Unless otherwise specified, a specification for a definite size or type of container or apparatus in a procedure is given solely as a recommendation. Other dimensions or types may be used if they are suitable for the intended use.

6.80.10. Apparatus for Measurement

Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed.

6.80.10.1. Pipet/Pipette

Where a pipet/pipette is specified, a suitable buret may be substituted. Where a "to contain" pipet/pipette is specified, a suitable volumetric flask may be substituted.

6.80.10.2. Light Protection

Where low-actinic or light-resistant containers are specified, either containers specially treated to protect contents from light or clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

6.80.20. Instrumental Apparatus

An instrument may be substituted for the specified instrument if the substitute uses the same fundamental principles of operation and is of equivalent or greater sensitivity and accuracy. These characteristics shall be qualified as appropriate. Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification.

6.80.20.1. Chromatographic Tubes and Columns

The term "diameter" refers to internal diameter (ID).

6.80.20.2. Tubing

The term "diameter" refers to outside diameter (OD).

6.80.20.3. Steam Bath

Where use of a steam bath is directed, use actively flowing steam or another regulated heat source controlled at an equivalent temperature.

6.80.20.4. Water Bath

A water bath requires vigorously boiling water unless otherwise specified.

6.80.30. Temperature Reading Devices

Temperature reading devices suitable for pharmacopeial tests conform to specifications that are traceable to an National Institute of Standards and Technology (NIST) standard or equivalent. Temperature reading devices may be of the liquid-in-glass type or an analog or digital temperature indicator type, such as a resistance temperature device, thermistor, or thermocouple. Standardization of thermometers is performed on an established testing frequency with a temperature standard traceable to NIST. For example, refer to the current issue of American Society of Testing and Materials (ASTM) standards E1 for liquid-in-glass thermometers.

Revision Bulletin

Official April 1, 2015

General Notices 7

7. TEST RESULTS

7.10. Interpretation of Requirements

Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated acceptance criteria to determine whether the article conforms to compendial requirements.

The reportable value, which often is a summary value for several individual determinations, is compared with the acceptance criteria. The reportable value is the end result of a completed measurement procedure, as documented.

Where acceptance criteria are expressed numerically herein through specification of an upper and/or lower limit, permitted values include the specified values themselves, but no values outside the limit(s). Acceptance criteria are considered significant to the last digit shown.

7.10.5. Nominal Concentrations in Equations

Where a "nominal concentration" is specified, calculate the concentration based on the label claim. In assay procedures, water correction is typically stated in the Definition and on the label of the USP Reference Standard. For other procedures, correction for assayed content, potency, or both is made prior to using the concentration in the equation provided in the monograph.

7.10.10. Equivalence Statements in Titrimetric Procedures

The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, the number of significant figures in the concentration of the titrant should be understood to correspond to the number of significant figures in the weight of the analyte. Corrections to calculations based on the blank determination are to be made for all titrimetric assays where appropriate (see *Titrimetry* (541)).

7.20. Rounding Rules

The observed or calculated values shall be rounded off to the number of decimal places that is in agreement with the limit expression. Numbers should not be rounded until the final calculations for the reportable value have been completed. Intermediate calculations (e.g., slope for linearity) may be rounded for reporting purposes, but the original (not rounded) value should be used for any additional required calculations. Acceptance criteria are fixed numbers and are not rounded.

When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is equal to or greater than 5, it is eliminated and the preceding digit is increased by 1.

8. TERMS AND DEFINITIONS

8.10. Abbreviations

- RS refers to a USP Reference Standard.
- CS refers to a Colorimetric Solution.
- TS refers to a Test Solution.
- VS refers to a Volumetric Solution that is standardized in accordance with directions given in the individual monograph or in the *Reagents, Indicators, and Solutions* section of *USP–NF*.

8.20. About

"About" indicates a quantity within 10%.

If the measurement is stated to be "accurately measured" or "accurately weighed," follow the statements in the general chapters *Volumetric Apparatus* (31) and *Balances* (41), respectively.

8.30. Alcohol Content

Percentages of alcohol, such as those under the heading *Alcohol Content*, refer to percentage by volume of C_2H_5OH at 15.56°. Where a formula, test, or assay calls for alcohol, ethyl alcohol, or ethanol, the *USP* monograph article Alcohol shall be used. Where reference is made to " C_2H_5OH ," absolute (100 percent) ethanol is intended. Where a procedure calls for dehydrated alcohol, alcohol absolute, or anhydrous alcohol, the *USP* monograph article Dehydrated Alcohol shall be used.

8.40. Atomic Weights

Atomic weights used in computing molecular weights and the factors in the assays and elsewhere are those established by the IUPAC Commission on Atomic Weights and Isotopic Abundances.

8.50. Blank Determinations

Where it is directed that "any necessary correction" be made by a blank determination, the determination shall be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

8.60. Concomitantly

"Concomitantly" denotes that the determinations or measurements are to be performed in immediate succession.

8.70. Desiccator

The instruction "in a desiccator" indicates use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of a suitable desiccant such as anhydrous calcium chloride, magnesium perchlorate, phosphorus pentoxide, or silica gel. See also section 8.220, *Vacuum Desiccator*.

8.80. Logarithms

Logarithms are to the base 10.

Illustration of Rounding Numerical Values
for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit $\geq 98.0\%$	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit $\leq 101.5\%$	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes
Limit test $\leq 0.02\%$	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤ 3 ppm	3.5 ppm	4 ppm	No
	3.4 ppm	3 ppm	Yes
	2.5 ppm	3 ppm	Yes

Revision Bulletin

Official April 1, 2015

General Notices 9

	Units	Symbol	Notes
	nanogram	ng	
	picogram	pg	
			Also referred to as the unified atomic mass unit and is equal to 1/12 times the mass of the free carbon 12 atom.
	dalton	Da	
	kilodalton	kDa	
Time			
	second	s	
	minute	min	
	hour	h	
Volume			
			1 L is equal to 1000 cm ³ (cubic centimeters)
	liter	L	
	deciliter	dL	
			1 mL is equal to 1 cm ³ , sometimes referred to as cc
	milliliter	mL	
	microliter	μL	
Temperature			
	Celsius	°C	
Amount of Substance			
			Historically referred to as gram-molecular weight or gram-atomic weight
	mole	mol	
	millimole	mmol	
	micromole	μmol	
	femtomole	fmol	
			Also referred to as gram-equivalent weight. It is used in the calculation of substance concentration in units of normality. This unit is no longer preferred for use in analytical chemistry or metrology.
	equivalent	Eq	
	milli-equivalent	mEq	
			Osmotic pressure of a solution, related to substance concentration.
	osmole	Osmol	
	milliosmole	mOsmol	
Pressure			
	pascal	Pa	
	kilopascal	kPa	
	pounds per square inch	psi	
	millimeter of mercury	mmHg	Equal to 133.322 Pa
Electrical Units			

	Units	Symbol	Notes
	ampere	A	
	volt	V	
	millivolt	mV	
	hertz	Hz	Unit of frequency
	kilohertz	kHz	
	megahertz	MHz	
	electron volt	eV	
	kilo-electron volt	keV	
	mega-electron volt	MeV	
Radiation			
	becquerel	Bq	SI unit of activity for radionuclides
	kilobecquerel	kBq	
	megabecquerel	MBq	
	gigabecquerel	GBq	
			Non-SI unit of activity for radionuclides
	curie	Ci	
	millicurie	mCi	
	microcurie	μCi	
	nanocurie	nCi	
Other			
	acceleration due to gravity	g _n	Used to express rate of centrifugation
	revolutions per minute	rpm	Used to express rate of centrifugation

Selected SI Prefixes

Name	Symbol	Factor
giga	G	10 ⁹
mega	M	10 ⁶
kilo	k	10 ³
deci	d	10 ⁻¹
centi	c	10 ⁻²
milli	m	10 ⁻³
micro	μ	10 ⁻⁶
nano	n	10 ⁻⁹
pico	p	10 ⁻¹²
femto	f	10 ⁻¹⁵

9. PRESCRIBING AND DISPENSING

9.10 Use of Metric Units

Prescriptions for compendial articles shall be written to state the quantity and/or strength desired in metric units unless otherwise indicated in the individual monograph (see also *Units of Potency [Biological]*, section 5.50.10 above). If an amount is prescribed by any other system of measurement, only an amount that is the metric equivalent of the prescribed amount shall be dispensed. Apothecary unit designations on labels and labeling shall not be used.

9.20 Changes in Volume

In the dispensing of prescription medications, slight changes in volume owing to variations in room temperatures may be disregarded.

10 General Notices

10. PRESERVATION, PACKAGING, STORAGE, AND LABELING

[NOTE—Storage- and packaging-related provisions previously addressed in the *General Notices* have been omitted, except for the brief provision proposed to be established below in 10.10; see general chapter *Packaging and Storage Requirements* (659) for packaging components and storage conditions. Labeling-related provisions are also in the process of being moved to a new general chapter *Labeling* (7), and will be similarly omitted in the future.]

10.10. Packaging and Storage

All articles in *USP* or *NF* are subject to the packaging and storage requirements specified in general chapter (659), unless different requirements are provided in a specific monograph.

10.40. Labeling

The term “labeling” designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term “label” designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in these compendia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the compendial requirements set forth for the articles.

10.40.10. Amount of Ingredient Per Dosage Unit

The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Official articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in *Deliverable Volume* (698). Official drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see 8.140, *Percentage Concentrations*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units. See also 5.50.10, *Units of Potency (Biological)*.

10.40.20. Use of Leading and Terminal Zeros

To help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than 1 shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

10.40.30. Labeling of Salts of Drugs

It is an established principle that official articles shall have only one official title. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids, but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

10.40.40. Labeling Vitamin-Containing Products

The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

10.40.50. Labeling Botanical-Containing Products

The label of an herb or other botanical intended for use as a dietary supplement bears the statement, “If you are pregnant or nursing a baby, seek the advice of a health professional before using this product.”

10.40.60. Labeling Parenteral and Topical Preparations

The label of a preparation intended for parenteral or topical use states the names of all added substances (see 5.20, *Added Substances* and see *Injections* (1), *Labeling*), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

10.40.70. Labeling Electrolytes

The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

10.40.80. Labeling Alcohol

The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C₂H₅OH.

10.40.90. Special Capsules and Tablets

The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it shall be used.

10.40.100. Expiration Date and Beyond-Use Date

The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., “EXP 6/08,” “Exp. June 08,” or “Expires 6/08”). [NOTE—For additional information and guidance, refer to the Consumer Healthcare Products Association’s *Voluntary Codes and Guidelines of the Self-Medication Industry*.]

The monographs for some preparations state how the expiration date that shall appear on the label shall be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is in-

Revision Bulletin

Official April 1, 2015

General Notices 11

tended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the compendial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article shall not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the *General Notices*. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution before use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the

absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) 1 year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be 1 year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser shall maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than 25°. The plastic material used in packaging the dosage forms shall afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records shall be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

10.40.100.1. Compounded Preparations

The label on the container or package of an official compounded preparation shall bear a beyond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, may be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* (795), *Stability Criteria and Beyond-Use Dating*).